ARCHIVES OF SURGERY

VOLUME 53 AUGUST 1946 NUMBER 2

COPYRIGHT, 1946, BY THE AMERICAN MEDICAL ASSOCIATION

SURGICAL APPROACH TO HYPERTENSION

Second Report

GEZA de TAKATS, M.D.

GUSTAV W. GRAUPNER, M.D.

EDSON F. FOWLER, M.D.
AND
ROBERT J. JENSIK, M.D.
CHICAGO

IN A previous report from the University of Illinois College of Medicine, de Takáts, Heyer and Keeton [1] presented the classification, the preoperative study, the selection of cases and the surgical procedures employed, together with the results of follow-up studies of hypertensive patients. Of the methods for splanchnic nerve section, the transdiaphragmatic method of Smithwick [2] gave by far the best results. The selection of patients with early hypertension and the use of this improved technic seemed to us the two important factors in the obtaining of good results. An attempt was also made to analyze the mechanism of relief in hypertensive patients after splanchnic section. Aside from the actual lowering of blood pressure, a slow, gradual improvement of cardiac and renal function, a postural hypotension with consecutive decrease in effective circulating blood volume and a decrease in reflex nervous irritability due to adrenal denervation were mentioned as contributing to the subjective and objective relief obtained.

In this report we wish to present additional experience with the transdiaphragmatic approach to the splanchnic nerves, which has now been performed on a total of 109 patients (table 1). The material is still small and undoubtedly will continue to remain so because of our increasingly rigid criteria for operability.

SELECTION OF PATIENTS FOR OPERATION

The preoperative study has been detailed in our first communication.[1] This has remained unchanged except that a simple practical work-up

From the Department of Surgery, University of Illinois College of Medicine, St. Luke's Hospital and Research and Educational Hospitals.

1. de Takáts, G.; Heyer, H. E., and Keeton, R. W.: The Surgical Approach to Hypertension, J. A. M. A. **118**:501 (Feb. 14) 1942.

2. Smithwick, R. H.: A Technique for Splanchnic Resection in Hypertension, Surgery **7**:1, 1940.

now consists of a three day period. On the first day, a basal metabolic rate and an electrocardiogram are obtained and blood is drawn for the determination of blood sugar, nonprotein nitrogen, urea nitrogen and cholesterol; blood counts, the sedimentation rate and a specimen of urine are obtained. An Addis count is done on the urine if the medical consultant thinks that it is indicated. The medical consultant sees the patient before and after the completion of the tests. The eye consultant describes the fundus, grades it and has the opportunity to reexamine it after the operation. Many photographs of fundi have been taken. The history, taken by the intern, checked by the resident and reexamined by the surgeon, is naturally interested in hereditary traits, in childhood diseases with manifest glomerulonephritis or pyelonephritis, in trauma to the lumbar region with manifest hematuria, in exposure to lead and arsenic and in other causes of recognizable renal damage. The neurogenic factor is carefully considered, and occasionally a neuropsychiatric consultation is held. The endocrine factor is evaluated,

TABLE 1.—*Number of Cases of Surgically Treated Hypertension During Ten Year Period*

Period	Years	Number of Cases
1	1934-1940	30 *
2	1940-1943	52
3	1944	27
Total		109 †

* J. A. M. A. **118**: 501, 1942
† Over 150 patients have follow-up records.

and pituitary, thyroid, adrenal and ovarian involvement is looked for. If obesity is present, a reduction in weight is attempted even if the patient seems operable. The significance of metabolic rates will be discussed later.

The second day is spent on studies of renal function. A concentration-dilution test, a fifteen minute phenolsulfonphthalein test and a urea clearance test are ordered. The Lashmet-Newburgh concentration test is valuable but places too much hardship on the patient, so that urinary concentration is carried out only overnight, from 6 p. m. to 9 a. m. An intravenous pyelogram and a roentgenogram of the chest, at a distance of 2 meters, are taken.

The third day, in which the study is usually completed by noon, is utilized to study the vasomotor reactivity of the patient. This includes the cold pressor test, the test with 9 grains (0.58 Gm.) of sodium amytal and the test for epinephrine and carbon dioxide sensitivity.[2a]

2a. Recently a pressor test by breath holding and a depressor test by combining hyperventilation with pressure on one carotid sinus have been added (Gubner, R.; Silverstone, F., and Ungerleider, H. E.: Range of Blood Pressure in Hypertension, J. A. M. A. **130**:325 [Feb. 9] 1946).

On the teaching service at the Research and Educational Hospitals, a number of other tests having teaching or research value are determined. With the help of the medical service of Dr. R. W. Keeton, whose interest in this problem has ben unfailing, glomerular filtration rate and total renal blood flow were determined by the inulin-diodrast clearance. Spinal fluid pressures are measured. Eyegrounds have been photographed before and after operation by Dr. R. W. Riser. Vital capacity is determined. All these methods may serve as a basis of a better understanding of the problems, but the short, two and one-half day, work-up is eminently satisfactory for the sizing up of the situation. We doubt that a prolonged study ever leads to any practical conclusion not reached by the short work-up.

The four grades of Wagener and Keith, as tabulated in our first communication, are closely followed. They need not be described again, since any one engaged in this work must be familiar with the classic monograph.[3] It has become increasingly clear, however, that a purely mechanical grading of hypertensive patients is fraught with pitfalls. A patient may have serious myocardial damage due to coronary occlusion and yet have grade 1 retinopathy or grade 1 renal involvement. Again, the renal involvement does not have to run parallel with retinal sclerosis. Aortic or arteriolar sclerosis may be more advanced than the visceral involvement. For this reason we have adopted, purely for our own intercommunications, the following grouping referring to operability.

The first group consists of persons in whom there is a clearcut indication for operation. The ages of these patients do not exceed 40 years. The younger they are the more progressive the disease is apt to be. Their family histories are often burdened with cases of hypertension. Their eyegrounds show no changes or slight narrowing of arterioles; arteriovenous compression may be present. Their systolic pressure varies from 200 to 150 mm. of mercury and the diastolic from 120 to 100; if they are below 20 years, a diastolic pressure of 90 is acceptable. The pressure comes down to normal at rest or during natural or artificial sleep induced with sodium amytal. The heart shows no or minimal changes, the urine is normal and all renal tests show normal function, with the exception of the inulin-diodrast clearance, which is extremely sensitive but is subject to a great deal of error.

This group is obviously the group 1 of Wagener and Keith, but in addition we include in it some of the early, adolescent hypertensive patients who are completely asymptomatic but have a bad family history and show exaggerated vasomotor reactivity. To this group belong

3. Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, Medicine **18**:317, 1939.

also a number of persons with transient hypertension, so clearly defined by Robert Levy and his associates.[4] Their careful follow-up of young persons who are vascular hyperreactors indicated that they were not good risks for the Army, nor do they do well in civilian life, as individual observations amply demonstrate.

CASE 1.—Fred W., 58 years old, has known of his hypertension since the age of 20. It was then noted that his blood pressure fluctuated a great deal and that it became normal on rest and rose on emotion, physical or mental stress. He smoked and drank rather heavily through his thirties. Early in his thirties attacks of gout began, severest in the spring, activated by alcoholic or dietary excesses. For twenty years he has been on a diet low in purine and has stopped drinking. His blood pressure still fluctuated, but the basal pressure at rest never dropped below 155 systolic and 90 diastolic, whereas it would rise to 180 systolic and 120 diastolic on many occasions.

On entrance to St. Luke's Hospital, July 5, 1943, the right foot was in a state of impending gangrene. It was swollen and cyanotic. The pedal pulses were absent on both sides. The histamine flares did not appear above the right ankle but did appear below the right knee. Paravertebral block with procaine hydrochloride relieved the pain but did not warm up the toes. Evidence of arteriosclerosis was found in the eyegrounds, in the heart and in the kidneys. However, the heart had not enlarged; while forty years after the onset of his hypertension he was still in the stage of benign nephrosclerosis, with hypertension which could still be lowered on rest, nevertheless the widespread vascular sclerosis may well be attributed to the hypertension of long standing.

Comment.—Such a history should be compared with the histories in cases of young hypertensive patients in their twenties who have undergone splanchnic nerve section; this would require a thirty to forty year follow-up of the surgical patients, which another generation of surgeons will have to publish. Suffice it to say that the fluctuating juvenile hypertension, even if it does not become malignant in its later stages or even if it does not reach excessive levels, may cause widespread vascular damage. The coronary sclerosis of this patient and the resulting myocardial damage may be responsible for the fact that after forty years his blood pressure is only moderately elevated. He now belongs in group 2.

Included in this first group are some of the patients who have more advanced vascular damage in the retina, the heart and the kidney but who relax under sodium amytal to a diastolic pressure of 100 mm. of mercury. The separation of such patients into one group has been brought about by the fact that when these persons have undergone a technically complete splanchnic section the results have been excellent. Seventeen patients have detailed follow-up records in this series.

---

4. Levy, R. L.; White, P. D.; Stroud, W. D., and Hillman, C. C.: Transient Hypertension: The Relative Prognostic Importance of Various Systolic and Diastolic Levels, J. A. M. A. **128**:1059 (Aug. 11) 1945.

The second group consists of patients in whom operability is debatable. The only argument for operating on these patients is the fact that some of them obtain unexpected objective and subjective relief whereas others have a slightly lower pressure, but the organic damage is naturally permanent and progressive. The advanced cases of group 2 and the early cases of group 3 of Wagener and Keith fall into this category. The ages of the patients may vary from 20 to 55; they have pronounced retinal sclerosis, recurrent angiospasm and even an occasional retinal hemorrhage. The diastolic pressure cannot be lowered below 110 mm. of mercury by any method. The heart is enlarged; there may be angina pectoris. The urine contains casts and albumin but no red cells. The Addis count is helpful in this group; a certain permissible number of red cells is always present by this method. The renal function is impaired, but urea clearance should not be below 50 per cent of normal. Cerebral accidents may already have occurred, with only temporary functional loss.

Obviously the patients in this group suffer from greater or smaller amounts of organic vascular damage. Twenty-eight patients have been operated on in this series; remarkable results have been obtained in a group of toxemic or eclamptic women in whom severe vascular damage occurred but in whom the damage did not continue to operate so that progress was arrested. Patients with healed glomerulonephritis or pyelonephritis with negative urinary findings and normal sedimentation rates may be included. In fact, only the renal biopsy reveals the origin of the hypertension. This special group of patients with renal hypertension will be discussed in more detail.

The third group consists of patients in whom splanchnic section is not indicated. To this group belong the late group 3 and all the group 4 patients of Wagener and Keith. Such patients have large recurrent hemorrhages or exudates in the retina; many of them have papilledema. The diastolic pressure is extremely high and may range from 170 to 120. It is fixed. Congestive or anginal cardiac failure is often present. The urine contains albumin, casts and red cells. The urea clearance is less than 50 per cent of normal and the concentrating ability of the kidney is below 1.015. Cerebral accidents have been numerous. The patient is in an actual or impending state of malignant hypertension. Five such patients have been operated on, and a large number of others have not been accepted for operation. No effect on the course of the disease was noted in this group.

To this group belongs also an important group of patients in whom some definite causative factor was responsible for the hypertension but could be readily overlooked. We have in mind 2 juvenile patients with hypertension referred to us for operation, who had coarctation of the

aorta. In 1 the femoral pulses were hardly palpable and erosion of the ribs was pronounced; in the other patient the diagnosis was less simple, since femoral pulses were good and the configuration of the aorta on roentgenologic examination was not typical. However, the difference in the oscillometric curves of the upper and lower extremities and the partial arterial block of the left subclavian artery led us to search for erosion of the ribs. Also a slight murmur in the left scapular region helped.

The presence of chronic or recurrent pyelonephritis equally contraindicates an operation. This is not to say that a completely "burned-out" lesion resulting in scarring and arteriolar sclerosis would not yield to operation, because we have such patients in our second group. It takes, however, an experienced and mature internist to detect these conditions, and often a diagnosis of essential hypertension is made since neither the history nor the urinary findings are suggestive. Smithwick [5] has just reported on a group of 11 pyelonephritic patients on whom splanchnic nerve section has been performed, with notable results. Attention should also be called to a large group of patients with slowly progressive hypertension suffering from arteriosclerosis of the aorta and its larger branches; they exhibit a high pulse pressure. They are not particularly suitable for operation, since the lowering of pressure will produce symptoms of decreased coronary or renal blood flow.

When the hypertension fluctuates greatly and is accompanied with rises in blood sugar, a chromaffin tumor of the adrenals can be suspected. The point should be stressed, however, that the fluctuating phase may later be followed by persistent hypertension, producing diffuse vascular damage.

Hypertension is often present in cases of tumors of the adrenal cortex and is especially suspected in cases of hirsutism, obesity and erythrocytosis. The attempts to differentiate these conditions from pituitary basophilism are not always successful. Whereas the ovaries can be palpated or inspected during exploration, the roentgenogram of the sella turcica and a sugar tolerance test are often unrevealing.

Both medullary and cortical adenomas may be encountered during the routine exploration of the kidney and adrenals, which is done at the time of the splanchnic section. The decision at this time to remove or resect a suspiciously large adrenal is not easy and if the operation is done it should be immediately followed by 20 cc. of adrenal cortex extract given intravenously. It should also be noted that both pituitary and

---

5. Smithwick, R. H.: Surgical Treatment of Hypertension: The Effect of Radical (Lumbodorsal) Splanchnicectomy on the Hypertensive State of 156 Patients Followed One to Five Years, Arch. Surg. **49**:180 (Sept.) 1944.

cortical adenomas producing neither sexual changes nor hypertension can be found at autopsy.

PREMEDICATION AND ANESTHESIA

In the present series all operations were done with identical technic. Premedication consisted of a light dose of barbiturate, such as 1.5 grains (0.09 Gm.) of pentobarbital sodium, for the night preceding the operation. One hour preceding the induction of anesthesia morphine-scopolamine was given in a 25 to 1 ratio, mostly 1/6 grain (0.01 Gm.) of morphine to 1/150 grain (0.0004 Gm.) of scopolamine. For women of slight build, weighing less than 125 pounds (56.7 Kg.), 1/8 grain (0.007 Gm.) of morphine to 1/200 grain (0.0003 Gm.) of scopolamine is preferable. The anesthetic preferred is ether administered intratracheally with the open drop method, with nitrous oxide and ether induction. In our earlier cases cyclopropane was used frequently, but too often cardiac irregularities were encountered on dissecting or pulling of the splanchnic nerves. In fact, because of reflexes originating from the stimulation of these nerves, the area can be advantageously flooded with 1 per cent procaine hydrochloride.

Because of the vicinity of the pleura and the necessity of separating pleural adhesions from the diaphragm or the posterior mediastinum, breathing must be even, not labored and not too deep. Also the accumulation of carbon dioxide must be prevented as much as possible. Such patients are definitely sensitive to the accumulation of carbon dioxide and respond with a rise in blood pressure and a pronounced venocapillary oozing. The oozing may be due to the peripheral action of carbon dioxide on blood vessels under deep anesthesia. Just as patients with toxic diffuse goiters require a great deal of oxygen and are exceedingly sensitive to the lack of it, hypertensive patients seem to tolerate the closed method with the absorption technic not so well as when drop ether is used with the tracheal tube in place or when a semiclosed ether-oxygen mixture is given without rebreathing and a flow of 10 liters of oxygen per minute is maintained. A one way valve is useful to blow off the expired carbon dioxide. With the cooperation of Dr. F. C. Jacobson, director of anesthesia at St. Luke's Hospital, we studied the reaction of some hypertensive patients to 10 per cent carbon dioxide administered for three minutes. The hyperventilation and rise in blood pressure were variable, but the sensitivity of some patients was pronounced and convulsive seizures or extreme restlessness necessitated the termination of the experiment (figs. 1, 2 and 3).

The problem of anoxia, hypercapnia and acapnia during such operations merits further study. Suffice it here to say that, as Gellhorn has shown for the experimental animal, the rise in carbon dioxide may

cause a pronounced rise in blood pressure in the lightly anesthetized or nonanesthetized patient, but the same concentration may cause a deep fall together with peripheral vasodilatation in the patient under deep narcosis.[6] That a pneumothorax accidentally produced may further complicate the situation by hypoventilation and inability to blow off the excess carbon dioxide seems obvious.

We have been impressed with the necessity of expert anesthesia and the closest interchange of ideas between a well trained anesthetist and the surgeon. In addition to maintenance of a free airway and control of the depth of anesthesia, the proper attention to signs of carbon dioxide accumulation are important. We have had our best exposures and favorable anatomic conditions greatly complicated by diffuse oozing, by hyperventilation and occasionally even by convulsions, which necessitated

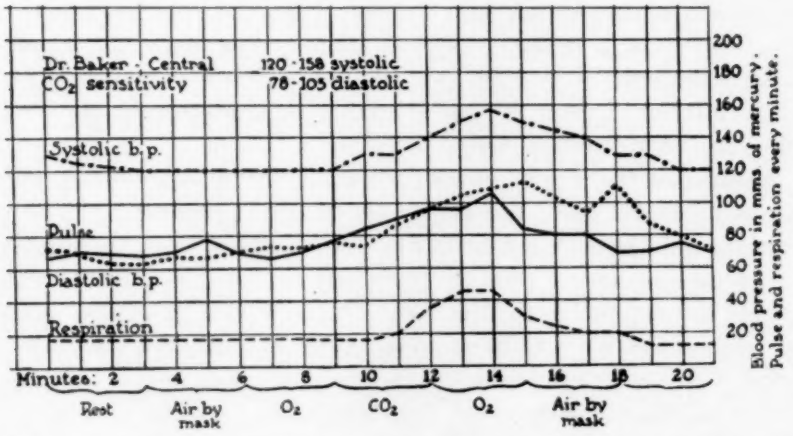


Fig. 1.—Pressor response to 7 per cent carbon dioxide in a young, normotensive man. After control periods with rest, air and oxygen by mask, none of which affected the patient's blood pressure, pulse rate or respiratory rate, carbon dioxide was administered for three minutes. Two minutes after the first whiff, all lines are seen to rise, the peak being reached two minutes after the carbon dioxide has been discontinued. This is a typical, normal response.

the postponement of some part of the operation to a later stage. Thus, in this series of 52 patients, the customary two stage operation had to be broken up into three stages in 3 patients because of conditions brought about by anesthesia.

Recently two timely articles have appeared on the importance of anesthesia during splanchnic nerve section. Haugen[7] recommended

6. Gellhorn, E. A.: Autonomic Regulations: Their Significance for Physiology, Psychology and Neuropsychiatry, New York, Interscience Publishers, Inc., 1943, pp. 23-27.

7. Haugen, F. M.: Hypertension: Management of the Anesthesia Period, Anesth. & Analg. **22**:152, 1943.

induction with 2.5 per cent pentothal sodium to facilitate induction and avoid the anoxemia during the stage of excitement; he also advocated the same drug when blood pressure rises because of carbon dioxide excess and after respiratory obstruction is relieved.

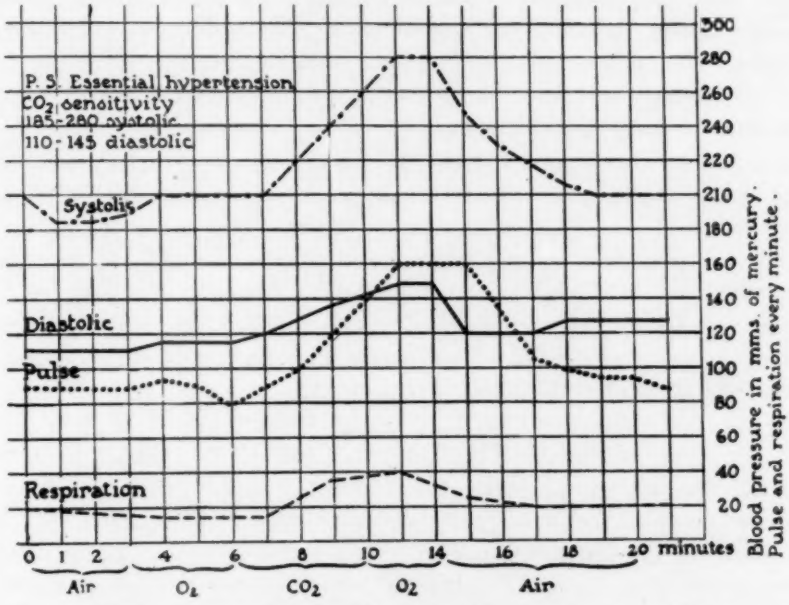

P. S. Essential hypertension
CO_2 sensitivity
185-280 systolic
110-145 diastolic
Systolic
Diastolic
Pulse
Respiration
0 1 2 4 6 8 10 14 16 18 20 minutes
Air O_2 CO_2 O_2 Air
Blood pressure in mms. of mercury.
Pulse and respiration every minute.
500 280 260 240 220 210 180 160 140 120 100 80 60 40 20

Fig. 2.—Pressor response to carbon dioxide. The same technic was used as in figure 1. Note the rise from 185 to 280 systolic and 110 to 145 diastolic pressures. The pulse rate rose from 110 to 160 a minute. This patient showed great sensitivity to carbon dioxide.

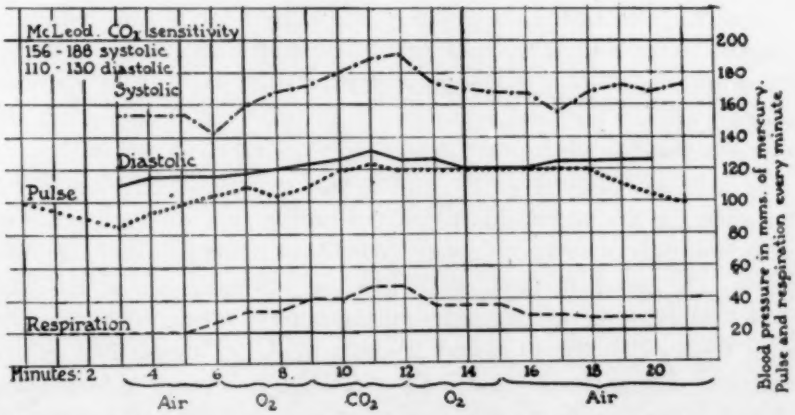

McLeod. CO_2 sensitivity
156-188 systolic
110-130 diastolic
Systolic
Diastolic
Pulse
Respiration
Minutes: 2 4 6 8 10 12 14 16 18 20
Air O_2 CO_2 O_2 Air
Blood pressure in mms. of mercury.
Pulse and respiration every minute.
200 180 160 140 120 100 80 60 40 20

Fig. 3.—The response of this patient showed little change from normal. His blood pressure showed little response to sympathectomy. The renal biopsy showed advanced nephrosclerosis with irreversible renal damage. While he was nervous and jittery and his condition was classified as "neurogenic" hypertension in another institution, his lesion at the time of operation was predominantly renal with severe vasoconstriction.

Phelps and Burdick [8] favored cyclopropane but mentioned that it may produce bronchospasm, which in turn is readily abolished by atropine, 1/150 grain (0.0004 Gm.) to 1/75 grain (0.0008 Gm.), given intravenously. We have had such an experience; changing to ether readily abolished the spasm. The authors also warned of rises of blood pressure during induction, during a stormy or prolonged second stage or from a disturbance of oxygen–carbon dioxide balance. Their article properly states that too little attention has been given to anesthetic procedures during surgical operations for hypertension.

This point requires emphasis because during conditions of war it has been necessary to operate with fewer expert anesthetists. If the surgeon has a good grasp of some of the principles involved, he may tide his patient over a critical situation. The anesthetist is such an important part of the surgical team that his absence or incompetence severely handicaps the operation. The fall in blood pressure occurring during various positions and immediately after section of the splanchnic nerves will be dealt with in the next paragraph.

THE COURSE OF THE OPERATION

After the patient has been intubated and his respiration and blood pressure stabilized, he is slowly turned over to a prone position. As is well known to anesthetists, this change of posture alone may bring about a further fall in pressure. In order to permit proper ventilation, a well inflated horseshoe cushion is placed on the table before the patient is rolled over from the cart. The break of the table, shown in figure 4*A*, has been lately abandoned, since it often contributes to a further fall in pressure and does not really facilitate exposure; it may help in resection of the twelfth rib. Instead of this position we now tilt the patient about 30 degrees to the side, with the surgical field raised toward the operator. This permits the flexion of the knee and hip of the side to be operated on, which relaxes the psoas muscle and greatly aids in removing the lumbar sympathetic chain from this angle.

The skin has been prepared with iodine and alcohol. Prior to the preparation the line of incision is marked on the skin with a 2 per cent aqueous solution of brilliant green (tetraethyldiaminotriphenylmethane sulfate). The incision starts at the level of the ninth rib at the well palpable outer border of the sacrospinalis muscle. After it reaches the level of the twelfth rib, it swings laterally along its course and gently curves toward the anterior-superior spine of the iliac bone, without quite reaching it. The skin marking is important since it obviates the palpation of the prepared skin for landmarks, which should be avoided. If the

8. Phelps, M. L., and Burdick, D. L.: Anesthetic Management of Patients Undergoing Sympathectomy for Hypertension, Anesthesiology **4**:361, 1943.

twelfth rib is not readily palpable because it is too short or the patient is too obese, it is well to have one of the pyelograms of the patient on hand, which readily denotes the length and course of the rib.

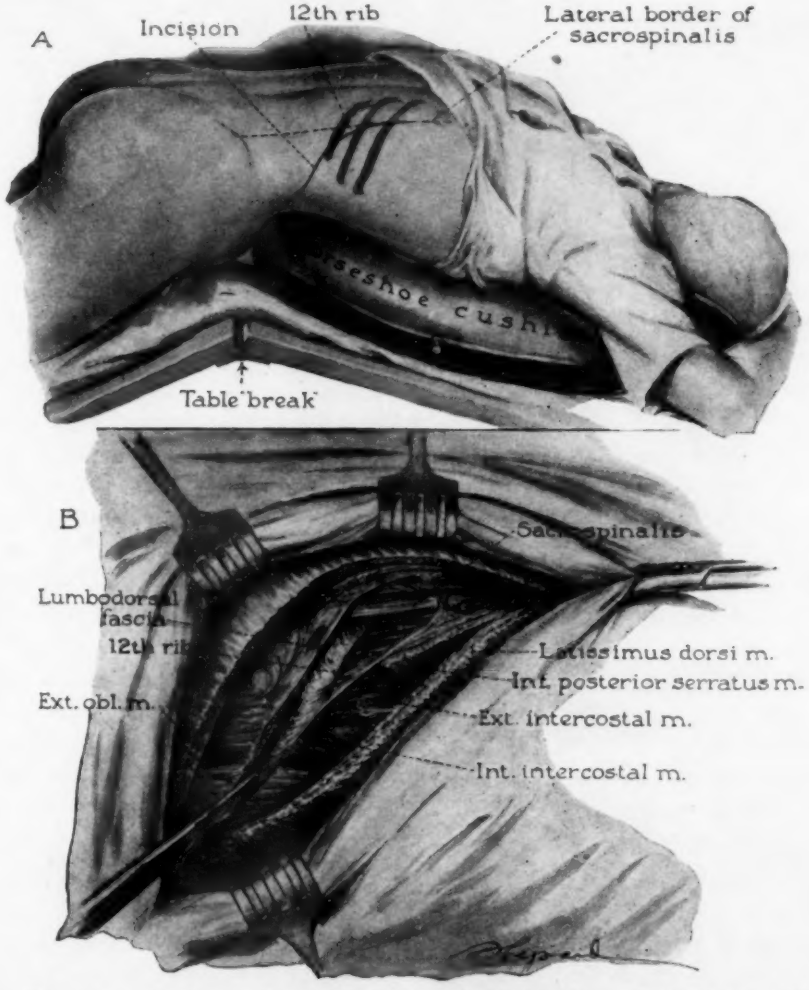


Fig. 4.—*A*, position of the patient on the operating table. An inflatable rubber cushion is placed below the chest, permitting expansion of the thoracic wall. The table is broken to develop the space between the twelfth rib and the iliac crest. The kidney rest is not elevated, as its pressure on the upper part of the abdomen often produces depressor reflexes and may also compress the vena cava, thus decreasing venous return to the heart. The incision starts at the palpable lateral border of the sacrospinalis muscle, follows the twelfth rib and curves gently toward the anterior-superior portion of the spine. *B*, the muscles of the back are cut along the line of the incision in the skin. The latissimus dorsi and the inferior posterior serratus muscles are well defined. Below them the lumbodorsal fascia is visualized. The incision is carried down to the twelfth rib. At the lower angle of the incision the oblique abdominal muscles become visible. Failure to identify and dissect these layers greatly handicaps adequate closure of the wound in layers.

To expose the twelfth rib the incision is carefully made through anatomic layers, since the reconstruction of the wound is thus facilitated (fig. 4*B*). The latissimus dorsi, the inferior posterior serratus muscle

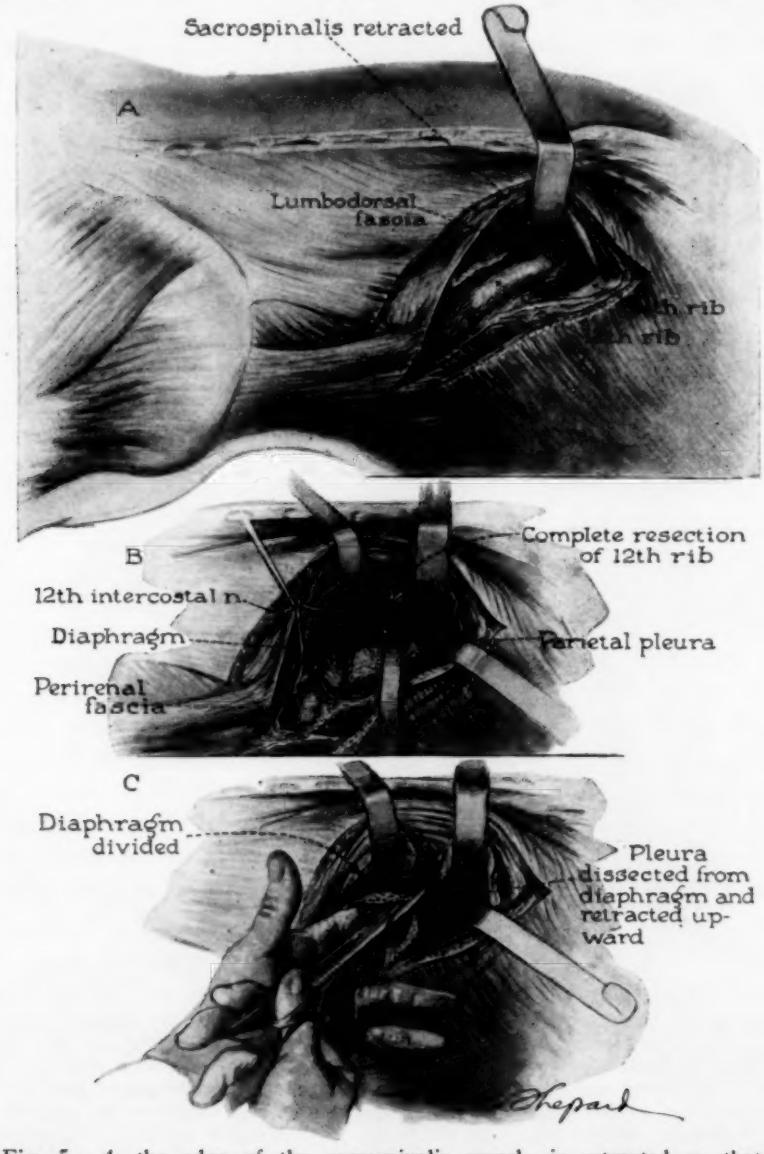


Fig. 5.—*A*, the edge of the sacrospinalis muscle is retracted so that the proximal end of the rib can be visualized. The twelfth rib is then resected from its tip to its articulation with the vertebra, which leaves a smooth articular surface. *B*, the resection of the rib is completed. At the lower angle of the wound the perirenal fat shines through the fascia. More medially the fibers of the diaphragm become visible. The pleura is often adherent to the diaphragm, and its edge should be carefully defined. *C*, the pleura has been bluntly pushed cephalad. The diaphragm is sectioned toward its vertebral attachment.

and the lumbodorsal fascia are divided. There is usually little bleeding unless the patient's venous pressure is high from straining or unless he is accumulating carbon dioxide under deep anesthesia. The edge of the sacrospinalis muscle is defined and mobilized, since retraction of this muscle toward the midline is important (fig. 5*A*). The twelfth rib is now removed in toto subperiosteally, by which we mean that the rib is exarticulated at the costovertebral joint. This leaves a smooth surface and allows better exposure of the thoracic sympathetic chain than if the rib is simply resected. After the removal of the rib, the pleura, the diaphragm and the perirenal fascia come into view. The twelfth intercostal nerve is resected from the lateral edge of the wound as close to the intervertebral foramen as possible (fig. 5*B*). The diaphragmatic pleura may be well defined as it spreads over the leaf of diaphragm, but it may also be obscured by adhesions, since a diaphragmatic pleurisy seems to be a remarkably frequent occurrence. The diaphragmatic pleura must be sharply or bluntly dissected from the diaphragm, since the diaphragm will have to be cut toward the spinal column, where the sympathetic chain and splanchnic nerves traverse it (fig. 5*C*). There are few bleeders in the diaphragm, which can be readily clipped with new silver clips. Cotton sutures may be placed as guy sutures and tied at the completion of the operation. The pleura now is peeled off the spinal column as high as the fingers of the operator will reach, thus exposing the posterior mediastinum. The anatomic structures which this operation must visualize are shown in figure 6*A*. When the parietal pleura is peeled off, the thoracic chain and splanchnic nerves become visible to the midthoracic level. The major splanchnic nerve can be seen to enter the celiac ganglion, which should also be visible. If the perirenal fascia and the peritoneum are peeled off, the lumbar sympathetic chain is exposed just medial to the psoas muscle. When the hip and knee are flexed and the patient is turned in a semilateral position, this exposure is greatly facilitated. The entire field is best exposed by four Deaver retractors, and a head lamp is used for illumination. The structures removed are shown in figure 6*B*. The major splanchnic nerve is clipped at the fifth or sixth thoracic level, a segment which cannot always be reached, because of adhesions or because of the shape of the thorax. As long a segment is excised as anatomically possible. Distally the nerve is transected at its entrance into the celiac ganglion. Often the minor and minimal splanchnic nerves are seen and cut, but no special effort is made to look for them, since the thoracic ganglions from which they originate are removed. The sympathetic ganglionated trunk is excised from the ninth dorsal to below the second lumbar ganglion. Clips are placed on the divided ends of the nerves to impede regeneration and also to enable a check on the level of transection by a roentgenogram.

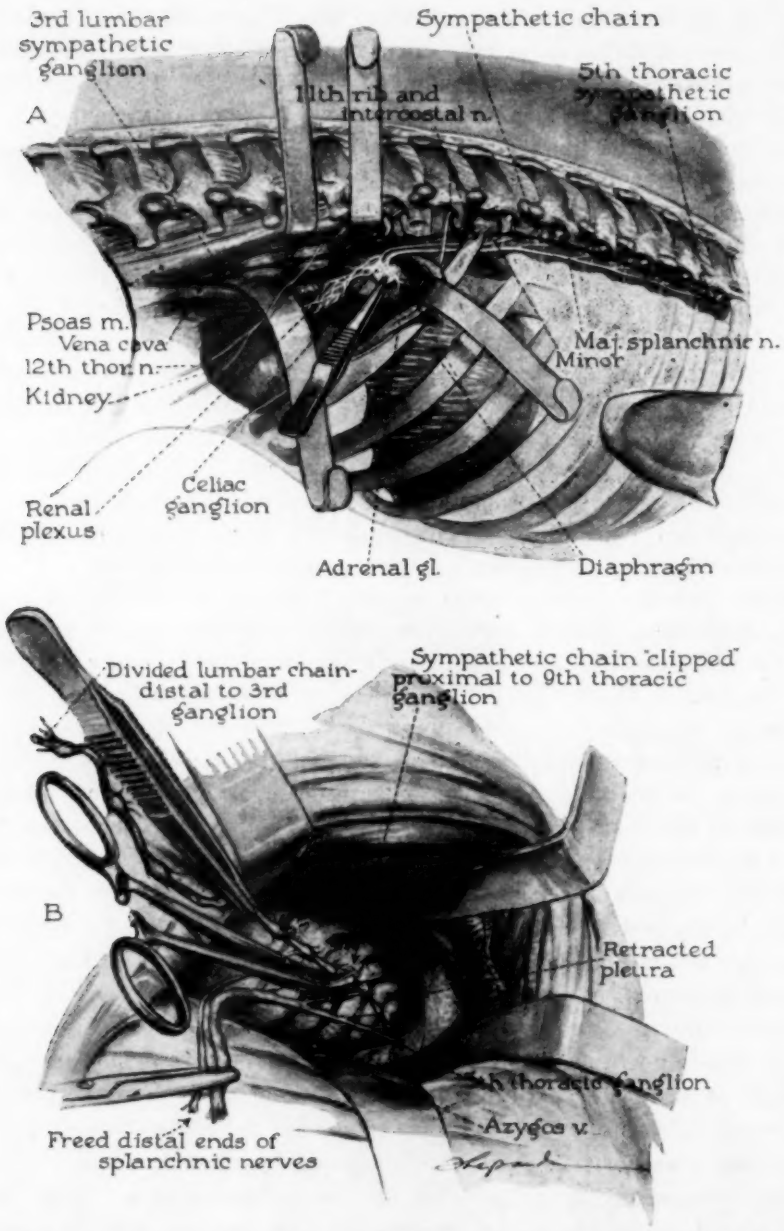


Fig. 6.—*A*, the anatomy of the splanchnic nerves and sympathetic chain as it is exposed in stages during the operation. The twelfth rib has been removed. The sympathetic chain and intervening ganglions are shown in black, and the splanchnic nerves are shown in white. The pleura, vena cava (on the right) and the psoas muscle are retracted. *B*, the actual operative procedure. The sympathetic chain is removed between the ninth dorsal and the third lumbar ganglion; the major splanchnic nerve from the fifth dorsal ganglion to its entrance into the celiac plexus. The diaphragm and kidney are not shown.

To facilitate exposure a part of the eleventh rib is resected when the twelfth is rudimentary.

Next the perirenal fascia is entered. The kidney is adequately exposed and its size, appearance and consistency noted. The renal pelvis and ureter, the renal vessels and the adrenal gland are palpated and if necessary exposed. Finally a long narrow pedicle is cut from the sacrospinalis muscle, an oval-shaped biopsy specimen is taken from the convexity of the kidney or wherever scarring or pitting is visible and three no. 20 cotton sutures are taken to secure the muscle flap into

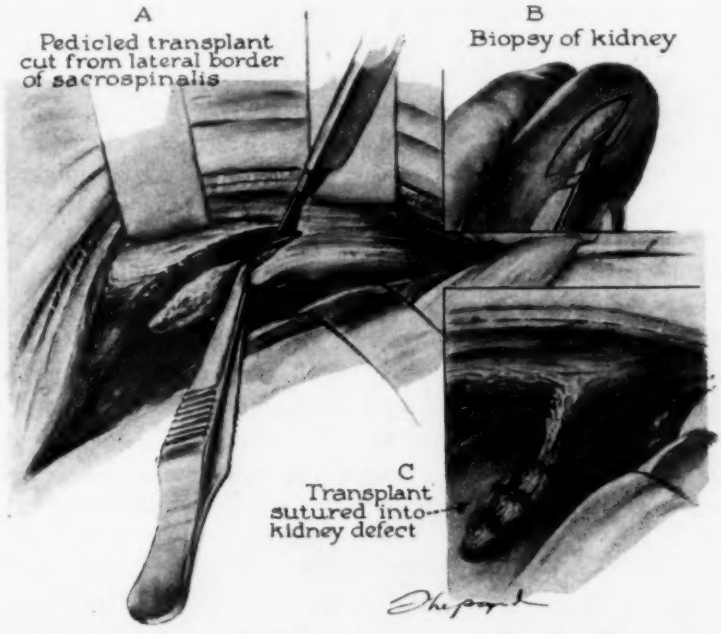


Fig. 7.—The kidney, ureter, renal artery and adrenal gland are palpated. An elliptic incision is made into the cortex of the kidney, and a previously prepared muscle flap is swung into the defect and anchored with three no. 20 cotton sutures. The muscle graft serves the triple purpose of hemostasis, nephropexy and possible revascularization through extrarenal channels.

the renal defect. This muscle graft not only stops bleeding but may serve as an avenue of collateral circulation [9] (fig. 7).

Naturally, if there is suggestive evidence in the preoperative studies of definite renal or adrenal involvement, the exploration of the kidney precedes the splanchnic section and the dorsolumbar sympathectomy.

The reconstruction of the wound is simple. No sutures are placed in the cut segment of the diaphragm, since frequent fluoroscopic studies

9. de Takats, G., and Scupham, G. W.: Revascularization of the Ischemic Kidney, Arch. Surg. **41**:1394 (Dec.) 1940.

have revealed no detectable impairment of respiratory function. In the earlier operations the muscle was sutured, which seems to account for more splinting and pain in respiration and possibly some pleural reaction. In suitable cases one may avoid cutting the diaphragm at all, by exposing the dorsal and lumbar chains above and below the diaphragm. This exposure, however, may necessitate the resection of the eleventh rib in addition. The cut muscles are sewed in three layers, and interrupted skin sutures are placed in the skin.

Throughout the operation isotonic solution of sodium chloride is administered intravenously. Unless an alarming fall in blood pressure occurs or a severe hemorrhage is encountered, no other fluid is given for the first stage, which is usually done on the right side. For the second stage, which is done from ten to twenty days after the first, from 500 to 1,000 cc. of blood are given routinely during the operation. While the drop in blood pressure after one splanchnic nerve has been cut is transitory, when the second nerve is cut a severe fall might occur, which is prevented or minimized by the transfusion of blood. Hemorrhage may be cumbersome from an intercostal vessel high up in the thoracic cavity when the dorsal chain is excised. Cushing clips carried on a 10 inch (25.4 cm.) long carrier readily arrest this bleeding. Occasionally hemorrhage may occur from an artery to the diaphragm which retracts, and such hemorrhage is difficult to control. If a tear in the pleura occurs, the operation may proceed without much difficulty except that careful reexpansion of the lung must be done when the wound is closed. Suction may be applied during closure. Small tears can be closed by Cushing clips or fine cotton sutures.

THE POSTOPERATIVE COURSE

Before the patient is returned to his room, signs of atelectasis are watched for. Whiffs of carbon dioxide are given to the patient every hour for twelve hours. He may move about freely. Usually 3,000 cc. of fluids are given intravenously the first day and 1,000 cc. the second day, on which the patient begins to take liquids. Morphine is given every six to eight hours to encourage ventilation and alleviate pain.

There has been no postoperative death in this series. Tension pneumothorax had to be aspirated in 3 cases, freeing the patient of respiratory distress. Subcutaneous emphysema developed and readily absorbed in a few cases. Pulmonary atelectasis was seen in 5 patients, bronchopneumonia developing in only 1. In 1 patient a late stitch abscess developed, which drained for six weeks. This patient had chronic acne of the back, which was treated with alcohol rubs and roentgen rays preoperatively, but it was obviously an error in judgment to proceed with the operation. The second side was done four months later,

without any difficulty. There were no other infections. No empyema developed in any of the patients with pneumothorax; fluid was allowed to absorb unless it caused respiratory distress.

Before the patient is discharged from the hospital, the presence or absence of postural hypotension is looked for. Also the signs of sympathetic denervation of both lower extremities are established. Unless this was pronounced, the operation was considered technically incomplete.[2] In older patients one lumbar chain is purposely left uncut. In some patients the preoperative studies are repeated, but this seemed an unnecessary imposition at this early date, so that studies were made only at three month intervals.

FOLLOW-UP SYSTEM

On discharge each patient receives copies of a questionnaire, which he is to mail in every three months the first year, every six months the second year and every year after that. The patients coming from the city of Chicago report in person; the out of town patients, who are mostly from downstate, are asked to have their referring physicians fill out the cards; most of them, however, return for one or two visits. The patients were reexamined in the vascular clinic of the University of Illinois College of Medicine or at St. Luke's Hospital.

The questionnaire was made as simple as possible, and many additional data were obtained on certain persons; this represents the

TABLE 2.—*Follow-Up Questionnaire for Patients Operated on for Hypertension*

Name.....		Date.....	
Address.....			
1. Have the following symptoms been	Relieved	Improved	Worse?
Fatigue.....	.....	.....	.....
Nervousness.....	.....	.....	.....
Dizziness.....	.....	.....	.....
Palpitation.....	.....	.....	.....
Breathlessness.....	.....	.....	.....
Urinary frequency.....	.....	.....	.....

2. What is your blood pressure after five minutes in the following positions:

Horizontal:..... Sitting:..... Standing:.....

3. What is the specific gravity of the urine in the morning? (Do not drink any fluid after 6 p. m. the night before.)

4. Are you working? Yes..... No.....

Full time..... Part time.....

If not working, is this due to your state of health?

minimal data obtained (table 2). Of the 52 patients living, records have been obtained of 50, which is the basis of the tabulated results.

TABLE 3.—*Results of Surgical Treatment of Hypertension (Grade 1)*

Case	Patient	Age, Yr.	Blood Pressure	Eye-grounds	Blood Pressure Under Sodium Amytal	Blood Pressure Under Vasoconstrictor	Blood Pressure in Horizontal Position	Postural Hypotension*	Symptoms	Working Ability †	Period of Follow-up, Mo.	General Result, on Basis of 3
					A. Males							
1	E. L.	23	181/121	1	120/80	.....	130/80	60/ ?	None	10 hr. day	48	1
2	J. W.	24	150/90	1	118/80	184/90	140/80	?/?	None	8 hr. day	25	1
3	S. R.	21	141/91	1	112/74	164/100	140/90	138/104	Palpitation; nervousness	8 hr. day	36	1
4	L. W.	28	146/74	0	110/56	.....	124/64	82/55	None	.....	18	1
5	J. G.	15	175/125	0	125/80	160/100	118/80	50/38	None	In Army	44	1
6	R. K.	24	150/90	0	120/65	.....	130/92	95/55	None	8 hr. day	46	1
7	G. L.	43	150/94	1	112/82	.....	140/100	123/92	None	8 hr. day	16	Incomplete lumbar sympathectomy
8	D. W.	20	160/66	1	116/70	236/100	120/80	120/75	None	8 hr. day	25	1
9	R. R.	20	160/80	0	118/70	.....	154/80	78/ ?	Few	11 hr. day	37	1
					B. Females							
10	M. C.	35	178/120	1	132/98	190/110	120/105	96/76	None	Sudden blindness; cerebral accident?	48	2
11	M. S.	24	146/112	0	126/84	.....	120/80	0	None	.....	56	1
12	J. W.	16	158/115	1	126/94	.....	156/100	.....	None	.....	51	1
13	M. Z.	21	152/99	0	135/80	190/120	140/80	80/ ?	.....	Dead	47	Went through pregnancy Sudden death; no cause
14	M. S.	25	152/95	1	120/76	.....	150/85	72/50	None	.....	36	1
15	D. T.	42	194/95	1	108/70	190/100	174/104	68/55	Slight headache	6 hr.	32	1
16	A. S.	33	153/100	1	122/70	166/122	120/85	84/56	Headache	Good	28	1
17	H. F.	23	135/90	0	100/80	140/95	128/100	60/0	Fatigue	.....	24	1

* Postural hypotension determined before discharge from hospital.

† Postoperative data are the ones obtained at time of last examination.

RESULTS OF THE OPERATION

The results of transdiaphragmatic splanchnic section have been studied separately in the three groups as defined previously.

Group 1 (table 3).—Seventeen patients have satisfactory follow-up records in this series, with postoperative periods ranging from eighteen to fifty-seven months. Their ages varied from 15 to 43, but with a few exceptions they were young, the average age being 27.3 years. Their preoperative blood pressures varied from 178 to 146 systolic and 120 to 74 diastolic. After an average follow-up period of thirty-five months, the blood pressures determined with the patients in the horizontal position were from 154 to 120 systolic; the diastolic pressure never exceeded 80 mm. of mercury. Each of these pressures represents the average of many individual determinations. Table 3 represents some of the data on this group of patients; the summary is given in table 4.

TABLE 4.—*Summary of Results of Surgical Treatment of Hypertension (Grade 1) in Seventeen Cases*

	Age, Years	Preoperative Blood Pressure, Mm. of Hg	Postoperative Blood Pressure, Mm. of Hg	Period of Follow-Up, Months
Maximum	43	178/120	154/80	57
Minimum	15	146/74	120/80	18
Average	27.3	157/97	144/80	35

From a study of these charts it would seem as if early, group 1, hypertension could really be checked and brought back to a normal level. While a preoperative diastolic pressure of 74 mm. is shown as the minimum, no patient was operated on who at one time or another did not show a diastolic pressure of 100 mm. of mercury.

In this group belong a number of patients with toxemic, rheumatic and pyelonephritic renal lesions which seem to show a favorable postoperative course, since the original injury to the vascular system of the kidney had subsided and the residual damage was not progressive; these groups will be discussed in more detail under a separate heading.

A few of the 17 case histories in brief abstract may serve better to illustrate the type of response to transdiaphragmatic splanchnic nerve section.

CASE 2 (table 3, case 1).—Edward L., a 23 year old laborer, was admitted to the Research and Education Hospitals on Oct. 3, 1940 to determine the cause of his hypertension, discovered during routine physical examination by his company physician. The patient was free of complaints on entrance.

Past History.—The patient had been well in every respect and able to carry on heavy manual labor. He had had scarlet fever in 1931. There was no history of renal complication.

* Postural hypotension determined before discharge from hospital.
† Postoperative data are the ones obtained at time of last examination.

On Entrance.—The patient's blood pressure was 192 systolic and 100 diastolic in millimeters of mercury. Pentothal sodium given intravenously reduced his blood pressure to 138 systolic and 90 diastolic in millimeters of mercury. Under 9 grains (0.58 Gm.) of sodium amytal the blood pressure fell to 120 systolic and 80 diastolic in millimeters of mercury. On bed rest his blood pressure varied between 190 and 120 mm. of mercury systolic and between 134 and 110 mm. of mercury diastolic. The physical examination was noncontributory. The eyegrounds showed evidence of slight spasm and early sclerosis of the retinal vessels. The urine was normal. Reactions to tests for renal function were within normal limits. An intravenous pyelogram was normal. The electrocardiogram showed no deformities. An insulin tolerance test showed a maximal depression to 86 mg. of glucose in 100 cc. of blood.

Operations.—Operations were done October 22 and October 29, the right and left splanchnic nerves and dorsolumbar sympathetic chains being excised.

Course.—On discharge the blood pressure in the horizontal position was 130 systolic and 80 diastolic in millimeters of mercury. On standing, the blood pressure was 60 systolic and 0 diastolic in millimeters of mercury. The insulin tolerance test showed a dip to 38 mg. per hundred cubic centimeters of blood. After two months of rest he resumed his previous work. The last follow-up, four years after operation, revealed that he was completely asymptomatic and worked ten hours daily in a defense plant. His blood pressure was 130 systolic and 80 diastolic in millimeters of mercury; the pressure dropped to 100 systolic and 60 diastolic on standing.

Comment.—This was a case of asymptomatic early hypertension. There was a history of scarlet fever. The patient has normal blood pressure, with full working capacity, four years after operation.

Case 3 (table 3 case 8).—Delano W., a 20 year old youth, entered the Research and Educational Hospitals of the University of Illinois College of Medicine on Jan. 21, 1942, complaining of shortness of breath, dizziness, fatigue and nervousness for the past eighteen months.

History.—The past history was noncontributory except for scarlet fever while the patient was in high school. The family history was noncontributory.

On Entrance.—The patient's blood pressure was 160 systolic and 86 diastolic in millimeters of mercury. The eyegrounds showed grade 1 retinopathy. The electrocardiogram showed a right ventricular preponderance; the roentgenogram of the chest, taken at a distance of 2 meters, showed the heart to be of normal size. The basal metabolic rate was + 8 per cent. Determinations of blood chemistry gave normal results. The urinary analysis was noncontributory. The phenolsulfonphthalein dye excretion in fifteen minutes was 30 per cent, the urea clearance (standard) was 88 cc. per minute. He concentrated urine to 1.037 specific gravity. The intravenous pyelogram was normal. Sodium amytal depressed the blood pressure from 160 systolic and 86 diastolic to 116 systolic and 70 diastolic. The epinephrine sensitivity test revealed a rise from 152 systolic and 80 diastolic to 236 systolic and 100 diastolic.

Operations.—Operations were performed on July 7 and July 21, 1942. Both splanchnic nerves were removed from midthoracic level to their entrance into the celiac ganglion. The sympathetic chain was removed from the twelfth dorsal to the second lumbar ganglion on the right and from the ninth to the twelfth dorsal ganglion on the left. On discharge the patient's blood pressure was 165 systolic

and 105 diastolic in the horizontal, 150 systolic and 100 diastolic in the sitting and 120 systolic and 75 diastolic in the standing position. The renal biopsy revealed grade 1 nephrosclerosis.

Course.—On Nov. 18, 1943 the patient was standing ten hours a day, as a postoffice clerk, behind the counter; the blood pressure of the patient in the horizonal position was 120 systolic and 80 diastolic, sitting 130 systolic and 90 diastolic and standing 130 systolic and 90 diastolic. The last follow-up, in October 1944, two years after operation, showed the patient at full work. The symptoms had disappeared. Blood pressure was 130 systolic and 70 diastolic in all three positions.

Comment.—This was a case of early hypertension, mostly systolic, with typical symptoms. The diastolic pressure of this patient only seldom reached 100 mm. The operation was not complete. (The chains were incompletely removed on either side.) There was no postural hypotension. The response of blood pressure to operation was not immediate, but a year and two years later the patient became asymptomatic and was at full work and his blood pressure was normal. This was a graded sympathectomy, with a good result up to date.

CASE 4 (table 3, case 13).—Margaret Z., a 21 year old unmarried woman, entered St. Luke's Hospital on June 15, 1941. With the exception of intermittent headaches, there were no complaints. One of these headaches was severe, lasted a whole day and was accompanied with nausea and vomiting. She had fallen from a horse several times; this was followed by dizziness for a day. There was some nycturia at times. She was rather highstrung, temperamental and readily upset.

On Entrance.—The patient's blood pressure was 160 systolic and 100 diastolic. The physical examination was noncontributory. The eyegrounds were normal. The heart occupied 40 per cent of the thorax. The electrocardiogram was normal. The urine was negative for pathologic elements. The intravenous pyelogram suggested a small and deformed left renal pelvis, but the retrograde pyelogram did not bear this out. The phenolsulphonphthalein excretion was 35 per cent in one hour; the urea clearance was 58 per cent (standard). Determinations of blood chemistry gave normal results. Sodium amytal depressed the blood pressure from 170 systolic and 104 diastolic to 135 systolic and 80 diastolic in millimeters of mercury. The cold pressor test raised it from 160 systolic and 100 diastolic to 190 systolic and 120 diastolic.

Operations.—Operations were done on June 26 and July 9, 1941, at which times a right and left splanchnic nerve section was done together with a dorsolumbar sympathectomy. Both chains were cut between the ninth dorsal and the second lumbar ganglion. The kidneys, ureters and adrenals were normal. A biopsy specimen taken from the right kidney revealed no pathologic changes.

Course.—The patient was discharged with blood pressures of 140 systolic and 80 diastolic, 120 systolic and 80 diastolic and 80 systolic and 0 diastolic in the three positions. The cold pressor response was minimal after the operation (140 systolic and 80 diastolic to 145 systolic and 80 diastolic). She continued to have occasional headaches but lived a healthy outdoor life, taking on the job of a wrangler on one of the western ranches. Her blood pressures fluctuated between 160 and 130 systolic and 100 to 80 diastolic during the next three years.

TABLE 5.—*Results of Surgical Treatment of Hypertension (Grade 2)*

Case	Patient	Age, Yr.	Pre-operative Blood Pressure	Eye-grounds	Blood Pressure Under Sodium Amytal	Blood Pressure Under Vasoconstrictor	Post-operative Blood Pressure	Postural Hypotension	Symptoms	Working Ability	Period of Follow-up, Mo.	General Result, on Basis of 3
					A. Males							
1	L. F.	17	191/114	1	168/100	210/140	148/90	90/50	None	8 hr. day	22	1
2	J. P.	25	180/120	1	160/100	.....	120/80	85/40	.....	Died	46	Died in mental institution
3	J. A.	31	210/134	2	140/110	240/180	145/105	90/60	None	.....	12	1-2
4	M. W.	31	220/120	2	138/96	216/120	190/130	110/100	Mild dizziness and palpitation	Good	8	1
5	G. P.	33	200/130	3	160/114	172/120	165/100	102/88	.....	.....	..	2
6	E. Mc.	39	200/135	1	156/120	210/154	170/110	90/50	.....	.....	..	2
7	F. F.	39	200/120	3	166/120	210/122	170/120	146/110	None	8 hr. day	18	2
8	J. T.	39	208/116	3	130/80	232/80	162/110	50/ ?	Dizziness and palpitation	8 hr. day	20	1
9	C. R.	42	255/115	3	170/90	.....	160/100	140/100	None	8 hr. day	..	1
10	L. R.	44	230/150	2	196/140	234/190	220/160	84/76	None	8 hr. day	22	2
11	R. F.	50	178/112	1	144/88	200/118	150/90	60/ ?	None	Good	15	1
12	J. C.	51	230/130	2	172/110	238/156	.....	.....	.....	.....	..	2
13	J. F.	52	215/120	2	142/92	.....	236/124	90/70	None	8 hr. day	14	2
					B. Females							
14	M. W.	28	184/130	1	154/98	252/156	170/102	130/ ?	Slight palpitation	8 hr. day	6	1
15	K. deT.	30	200/110	2	166/118	236/170	140/110	80/ ?	Some dizziness and palpitation	Fair	30	2
16	L. T.	33	210/150	1	130/110	240/162	.....	115/85	.....	.....	..	2
17	A. B.	33	180/110	1	134/82	180/115	186/130	138/80	Headache	.....	30	1
18	M. H.	34	200/120	1	150/100	250/150	170/124	165/100	None	8 hr. day	22	Unrelated symptoms
19	A. M.	34	250/170	..	.....	.....	200/130	160/120	.....	.....	9	2
20	A. K.	34	190/120	0	.....	.....	180/110	150/98	None	.....	22	1
21	A. S.	39	220/140	2	152/110	225/135	160/100	100/70	.....	.....	..	1
22	M. D.	40	210/130	1	172/120	242/140	182/116	132/98	.....	.....	17	2
23	M. W.	46	160/118	1	138/104	170/100	145/95	94/ ?	Slight palpitation	8 hr. day Died; sudden collapse; autopsy noncontributory	21	1
24	C. B.	48	256/150	1	170/110	286/164	235/120	108/78	Same	Fair	4	2

Postural hypotension had disappeared. In May 1944 she had a spell of unconsciousness, with a blood pressure of 90 systolic and 60 diastolic in millimeters of mercury, from which she temporarily recovered, but she died suddenly in a second attack, on May 28, 1944, not quite three years after operation. At autopsy (Dr. Foster and Dr. Hildebrand, Community Hospital, Geneva, Ill., No. 25270) no anatomic cause for death was found. The kidneys both grossly and microscopically were normal. Nothing was found in the brain.

Comment.—This is a case of nonrenal hypertension for which no cause could be found at autopsy. Note that a complete splanchnic section did not materially influence the blood pressure for the follow-up period of three years. This observation will be later discussed on the basis of other cases of "neurogenic" hypertension.

Group 2.—Twenty-four patients were available for study. This is a heterogeneous group in which organic vascular damage is definite, but vasomotor relaxation still produces a lowering of blood pressure, although not to a normal level. This group contains the group 2 and the earlier cases of group 3 of the Keith-Wagener classification. Operation has been definitely worth while in some and showed no result in others. Some patients have died, and the careful analysis of their histories has revealed some mistakes in indications or surgical technic (table 5). The ages of the patients in this group varied between 17 and 52 years; the preoperative blood pressure fluctuated between 256 and 160 systolic and 150 and 118 diastolic expressed in millimeters of mercury. The average preoperative blood pressure was 207 systolic and 128 diastolic in millimeters of mercury; this was depressed to an average of 176 systolic and 110 diastolic in millimeters of mercury, although in individual cases as low a level as 120 systolic and 80 diastolic could be reached. The average period of follow-up was 18.8 months, although a few patients have been followed as long as four years (table 6).

Case 5 (table 5, case 1).—John P., a 25 year old punch press operator, was admitted to the Research and Educational Hospital, complaining of pain and ulceration of toes, blueness of fingers in both hands, dizzy spells and nervousness.

Table 6.—*Summary of Results of Surgical Treatment of Hypertension (Grade 2) in Twenty-Four Cases*

	Age, Years	Preoperative Blood Pressure, Mm. of Hg	Postoperative Blood Pressure, Mm. of Hg	Period of Follow-up, Months
Maximum	52	256/150	236/124	55
Minimum	17	160/118	120/80	13
Average	37.2	207/128	176/110	27.8

Past History.—He was well until September 1939, when pain appeared in the right fifth toe. After heat and roentgen ray therapy, the skin broke down and

chronic ulcers developed. The patient lost his job. His fingers became cyanotic; he lost 35 pounds (16 Kg.) in the last year because of intractable pain in the extremities. There was angina pectoris on effort.

On Entrance.—The retinal vessels were narrow and tortuous and showed arteriovenous nicking. Blood pressure was 182 systolic and 122 diastolic in millimeters of mercury. The electrocardiogram showed myocardial damage. Urea clearance was 30.2 cc. per minute; the urea ratio was 44. Split kidney function showed delay in the appearance of the dye, chiefly on the left. Intravenous pyelograms were normal.

The distal phalanges of all fingers except the thumbs were cold and cyanotic; so were the toes. The left third toe had been previously amputated at the distal phalanx; the nail of the fourth toe had been removed and the fifth toe was gangrenous. A diagnosis of diffuse arteriolar disease with hypertension was made. Biopsy of muscle showed capillary stasis and arteriolar sclerosis. No evidence of periarteritis nodosa or thromboangiitis obliterans was found. The organic vascular damage was severe and diffuse.

Operations.—Operations were performed as follows: left and right cervicodorsal sympathectomy on Nov. 11, 1939, left lumbar sympathectomy on Dec. 5, 1939, right lumbar sympathectomy with removal of a renal biopsy specimen on Jan. 23, 1940, left transdiaphragmatic splanchnic nerve section on Feb. 12, 1940, and right transdiaphragmatic splanchnic nerve section on Aug. 16, 1940.

Course.—The cyanosis, pain and ulceration of the extremities were relieved. The anginal pain disappeared. The blood pressure at first did not drop below 160 systolic and 100 diastolic in millimeters of mercury; however, with the patient in the erect position it was 85 systolic and 40 diastolic in millimeters of mercury. Standing still for five minutes produced dizziness; however, headaches and nervousness were relieved. Two months after operation the blood pressure was 115 systolic and 80 diastolic with the patient in the horizontal position and was inaudible in the vertical position. Amphetamine relieved the symptoms of postural hypotension. Four months after operation the horizontal and vertical pressures were almost the same. Six months postoperatively he was back at full work. Eight months after operation the blood pressure was 120 systolic and 80 diastolic in millimeters of mercury while the patient was lying down and 95 systolic and 70 diastolic in millimeters of mercury after he had stood for five minutes.

The histologic picture of the renal biopsy specimen (Dr. S. R. Rosenthal) revealed strikingly well preserved glomeruli, compared with the almost total destruction of tubules. These were replaced by dense fibrous tissue; rarely a tortuous dilated tubule was filled with casts. There was increase of fibrosis in the interstitial tissue, which was interspaced by numerous round cells. The latter formed nodules at focal points. The arterioles were greatly thickened as a result of intimal proliferation. The lumens were frequently completely obliterated or canalized. The arteries showed thickening of the intima and media but no obturation of the lumen. The impression was that of a secondary contracted kidney, probably a pyelonephritic kidney. Renal involvement was grade 3.

In spite of the almost complete sympathectomy (first to fourth dorsal and sixth dorsal to third lumbar ganglions on each side, with both major splanchnic nerves excised), there were motile spermatozoa in a fresh condom specimen.

This case has been previously reported by Helfrich and one of us.[10] The patient made repeated visits to the surgical dispensary; his blood pressure did not go above 130 systolic and 90 diastolic at any time. However, he began to show evidence of organic disease of the brain with dementia, although no acute episode occurred. He entered the Elgin State Hospital, where he died on Sept. 9, 1943. At autopsy (Dr. A. Lieberman) the significant findings were as follows: terminal hemorrhagic infarct in the left lower lobe of the lung and small, contracted kidneys with a fine mottled surface. Grayish brown areas of fibrosis alternated with hemorrhagic zones in the cut section. The renal arteries were patent. The heart showed an old infarction at the apex and a concentric hypertrophy. The brain appeared to be smaller than normal. There were a number of yellowish areas of softening, most pronounced in the left motor area. The left frontal lobe was unusually congested. There was a moderate degree of arteriosclerosis of the basal vessels. Histologic sections were not available to us for study.

Comment.—This was the case of a young man with severe diffuse arteriolar sclerosis of unknown origin. He certainly did not present the picture of a typical essential hypertension; in fact, his complaints were first related to the peripheral vessels. The renal biopsy, performed in 1940, was suggestive of pyelonephritis; yet three years later he did not die of malignant nephrosclerosis but of encephalomalacia. The patient, although the hypertension was relieved, had irreparable and progressive arteriolar damage and would not be considered operable under our present indications. Note that even an almost total sympathectomy is not capable of arresting the progress of this type of disease. It may have been due to lead intoxication or some other vascular poison.

Case 6.—James T., a 39 year old farmer, was admitted to St. Luke's Hospital on March 19, 1942, complaining of severe occipital headaches for three years and progressive dyspnea on exertion for eight years. His heart palpitated occasionally. He was entirely incapacitated.

Past History.—The patient was well until eight years ago, when headache and dyspnea first developed. His blood pressure was not determined until six months ago, at which time it was 175 mm. of mercury (no doubt, systolic). There was no family history of hypertension and no history of renal disease in childhood.

On Entrance.—The patient's blood pressure was 208 systolic and 116 diastolic and varied at rest between 222 systolic and 135 diastolic and 176 systolic and 120 diastolic in millimeters of mercury. The eyegrounds revealed vasospastic retinopathy, with old hemorrhages and exudates, and a grade 3 fundus. The heart occupied 41 per cent of the thorax. An electrocardiogram revealed myocardial damage; there was some angina on effort. The basal metabolic rate was +7 per cent. The urine persistently contained albumin (4 plus); the phenolsulfonphthalein excretion was 15 per cent in fifteen minutes. The urea clearance was 29.2 cc. (standard); he concentrated urine to 1.020. On administration of sodium amytal his pressure dropped from 180 systolic and 120 diastolic to

10. de Takats, G., and Helfrich, L. S.: Sterility of the Male After Sympathectomies, J. A. M. A. **117**:20 (July 5) 1941.

130 systolic and 80 diastolic; the cold pressor test revealed no rise. Epinephrine raised his pressure from 174 systolic and 94 diastolic to 232 systolic and 80 diastolic in millimeters of mercury. When his vascular status is sized up, the greatest damage seemed to be in the kidney and eyegrounds and less in the heart and peripheral vascular tree.

Operations.—Operations were performed on May 27 and June 15, 1942, at which times right and left transdiaphragmatic splanchnic nerve section and dorsolumbar sympathectomy from the ninth dorsal to the second lumbar ganglion were done. The renal biopsy revealed severe nephrosclerosis with narrow arteriolar lumens and hyaline changes in glomeruli and tubules. It was grade 3 nephropathy. The patient left the hospital with a blood pressure of 168 systolic and 92 diastolic, 130 systolic and 90 diastolic and 50 systolic and undetermined diastolic in the three positions. His postural dizziness and dyspnea were pronounced.

Course.—Although the patient lived in Arkansas, excellent follow-up records were obtained through the courtesy of Dr. L. L. Hubener. A year and a half after the operation his blood pressures were 160 systolic and 110 diastolic, 165 systolic and 110 diastolic and 150 systolic and 100 diastolic in the horizontal, sitting and standing positions. The pressure dropped to 135 systolic and 95 diastolic after exercise. He lost his headache and dizziness but had palpitation and was able to work full time except that he reported periods of incapacity, pointing to cardiac strain. The urine was concentrated to 1.020, with a faint trace of albumin and occasional pus cells. Two and a half years after operation he was living comfortably on a reduced physical schedule. His blood pressure varied from 165 to 150 systolic and 110 to 100 diastolic.[10a]

Comment.—This is a patient with severe organic damage but enough vasospasm so that the operation resulted in decided benefit. He was restored to a limited activity. His symptoms have subsided. It is doubtful whether his life expectancy has been greatly prolonged, but up to date, four years since the operation, his blood pressures have been lowered consistently and have not shown any tendency to rise.

Group 3.—Ten patients belong to this group (table 7). Their ages varied from 7 to 52 years. Their preoperative blood pressure varied from a maximum of 265 systolic and 155 diastolic to a minimum of 200 systolic and 170 diastolic, with an average of 234 systolic and 158 diastolic in millimeters of mercury. The average postoperative blood pressure was 210 systolic and 153 diastolic in millimeters of mercury, indicating no hypotensive effect. While there was no surgical mortality, all patients died within a year of the operation.

This is an extremely important group, since on the basis of our early experience with this type of patient we regard the patients in this group as entirely inoperable. The group includes not only patients in the malignant phase of hypertension but some of the late group 3 patients of the Keith-Wagener classification who have no papilledema and no necrotizing arterioles but who have retinal hemorrhages, poor

10a. Four years after operation, his blood pressure varied from 160 to 150 systolic and 110 to 100 diastolic.

TABLE 7.—*Results of Surgical Treatment of Hypertension (Grade 3)**

Case	Patient	Age, Yr.	Pre-operative Blood Pressure	Eye-grounds	Blood Pressure Under Sodium Amytal	Blood Pressure Under Vasoconstrictor	Post-operative Blood Pressure	Postural Hypotension	Symptoms	Result	Period of Follow-up, Mo.	Autopsy
					A. Males							
1	F. P.	29	246/168	3	Not done	246/168	238/160	None	Hypertensive; uremic	Died	4	Malignant nephrosclerosis
2	H. K.	52	247/140	2	180/110	.....	Not operated on	.....	Vascular accident	Died	4	
					B. Females							
3	S. S.	7	200/170	4	Not done	.....	190/160	None	Same	Died	2	Congenital hypoplastic kidney
4	J. H.	7	240/190	4	200/160	.....	Not operated on	.....	Uremia; vascular accident	Died	6	Malignant phase; congenital hypoplastic kidney
5	P. B.	7	225/160	1	Not done	.....	180/150	.....	Same	Died	2	
6	B. H.	21	230/142	4	230/142	.....	210/140	None	Same	Died	2	
7	E. H.	29	242/168	2-3	214/160	250/168	200/160	178/150	Same	Died	2	
8	C. S.	25	220/150	4	Not done	230/150	Not operated on	.....	Same	Died	2	
9	A. J.	39	265/155	3	150/90	250/170	Not operated on	.....	Same	Died	91	Not included in average
10	H. W.	27	230/140	2	156/106	250/147	240/145	None	Same	Died	..	Not included in average

* In cases 1, 3 and 9 bilateral nephro-omentopexy was performed in addition to splanchnic section; in case 7 a nephrectomy was performed. Blood pressure as quoted is the average of maximum and minimum pressures obtained.

cardiac and renal reserve and fixed blood pressures, which hardly respond in any direction (table 8).

CASE 7 (not included in the tabulated series).—The history of case 7 was published in a previous communication.[1] Carmela S., a 25 year old married woman,

TABLE 8.—*Summary of Results of Surgical Treatment of Hypertension (Grade 3) in Ten Cases*

	Age, Years	Preoperative Blood Pressure, Mm. of Hg	Postoperative Blood Pressure, Mm. of Hg.	Period of Follow-up, Months
Maximum	52	265/155	240/145	All 10 died, 9 within a year and 1 five years after operation
Minimum	7	200/170	180/150	
Average	24.3	234/158	210/153	

was admitted to St. Luke's Hospital on May 23, 1940, complaining of intractable headaches and vertigo of one year's duration.

Past History.—She suffered from mild headaches all her life. Four years previously, while pregnant, she was told of her high blood pressure. The delivery was uneventful, as she had been allowed to carry the baby to term, but two days after delivery eclampsia developed. The blood pressure never came down to normal. Aching in the eyeballs and headaches increased in severity. Two weeks before her entrance to the hospital, the patient became dizzy and fainted.

On Entrance.—Pronounced hypertensive retinopathy was found, with blurred disks, exudates and hemorrhages. The blood pressure varied from 230 to 210 systolic and 158 to 140 diastolic in millimeters of mercury. The heart was moderately enlarged to the left. The electrocardiogram showed myocardial damage. Renal function was poor, with a standard urea clearance of 15.3 cc. The urine contained less than 50 mg. of albumin but occasional red cells. There was no nitrogenous retention. The intravenous pyelogram was normal. The responses to cold, to epinephrine and to sodium amytal were slight. A diagnosis of posteclamptic hypertension terminating in malignant nephrosclerosis was made. Operation was not advised.

Course.—The intractable headaches were not influenced by irradiation of the pituitary. Sudden death occurred two months after discharge, presumably from massive intraventricular hemorrhage. Autopsy was not done.

Comment.—There can hardly be any doubt that such a patient cannot be benefited by operation, and there is fair unanimity among surgeons that such patients are inoperable. All our patients belonging to this group died; our attempts at a revascularization of the kidney by implanting omentum or muscle have equally been unsuccessful.[9]

CASE 8 (case 6 in table 7).—Betty H., a 21 year old married woman, entered the Research and Educational Hospitals on Nov. 2, 1939, complaining of severe continuous headache, nausea, vomiting and severe pain in the chest lasting for two weeks.

Past History.—She was well up to the age of 17, when four months after being married she had a miscarriage. Her physician told her that she would never have a full term baby. A few months later she again became pregnant; she was told of her high blood pressure and albumin in the urine. Her feet

were swollen. Labor was induced, and she was unconscious for two days. A year later she had continuous headaches and then again became pregnant. She lost this baby around the third month. After this, nausea and vomiting were frequent. In April 1939 paralysis of the right facial nerve occurred, and in September 1939 paralysis of the left facial nerve developed. Severe knifelike pain appeared under the left costal margin. She did not know whether her pressure fell or not during this time.

On Entrance.—Both eyegrounds showed papilledema, exudates and hemorrhages. Blood pressure varied from 250 to 210 systolic and from 150 to 136 diastolic in millimeters of mercury. Neither pentothal sodium given intravenously nor sodium nitrite or sodium amytal administered orally were able to depress the diastolic pressure below 140 mm. of mercury. Potassium thiocyanate was ineffective. Renal function was greatly impaired, the urea clearance being depressed to 15 cc. per minute but with no nitrogenous retention. The urine showed red blood cells and casts, with 0.2 to 1.4 Gm. of albumin daily. The heart was enlarged, and the electrocardiogram showed evidence of myocardial damage.

Operations.—Operations on Jan. 2 and Jan. 23, 1940 consisted of bilateral supradiaphragmatic section of the splanchnic nerves. On discharge the blood pressure had reached its preoperative level. She died at home, suddenly, two months later.

Comment.—The past history of this young woman is pitiful. She should have been sterilized after her first miscarriage because of the toxemic hypertension. As will be discussed later, our results in patients with post-toxemic hypertension have been favorable when the original vascular injury does not repeat itself. In this patient three pregnancies produced, in the course of four years, malignant nephrosclerosis. We operated on some patients of this type four to five years ago, on the plea of the internists that they are young, that they resist medical treatment and that they are otherwise lost. Our experience has been that no type of operation, whether extensive splanchnic section or muscle transplants to the kidney, can save such patients. This stage should be regarded as contraindicating operation.

While there is fair agreement about the malignancy and intractability of hypertension in such patients, we wish to present another group in whom we have been unable to modify the course of the disease and who therefore have not been subjected to operation in the last few years.

CASE 9.—John F., a 52 year old switchman, entered St. Luke's Hospital on Sept. 13, 1942, complaining of dizzy spells, headaches and palpitation. He had known of his hypertension for six years.

Past History.—A doctor discovered that the man had high blood pressure six years ago, but the patient was asymptomatic at the time. Two years ago a diagnosis of essential hypertension was made, and the patient was given potassium thiocyanate. Under this drug the lowest blood pressure obtained was 150 systolic and 90 diastolic in millimeters of mercury. The blood pressure in the right arm was persistently 15 to 20 mm. of mercury lower than that in the left arm. In the past few months the symptoms have been severer.

On Entrance.—The patient's blood pressure was 226 systolic and 130 diastolic in millimeters of mercury. The eyegrounds revealed a mild narrowing of the retinal arteries, with pronounced nicking of the veins. The heart occupied 40 per cent of the thorax. The thoracic aorta was tortuous and calcified. An electrocardiogram revealed mild myocardial damage. An intravenous pyelogram was normal. He concentrated urine between 1.002 and 1.020; the urea clearance was 53.1 cc. (standard). Under administration of sodium amytal the pressure in the right arm fell from 182 systolic and 110 diastolic to 156 systolic and 90 diastolic. In the left arm it fell from 230 systolic and 130 diastolic to 142 systolic and 92 diastolic.

Operations.—Operations were done on Sept. 21 and Oct. 24, 1942. During the first stage an epiglottic retention cyst was removed, which was discovered on intubation. The second stage was followed by a stormy course. On the third postoperative day the patient had an attack of severe retrosternal pain, dyspnea and cyanosis; the blood pressure dropped to 80 systolic and 60 diastolic in millimeters of mercury. The patient responded well to our routine therapy for pulmonary embolism; this diagnosis was considered most likely, since the electrocardiogram revealed minimal changes from the preoperative one. The patient left the hospital with pressures of 170 systolic and 100 diastolic, 180 systolic and 100 diastolic and 90 systolic and 70 diastolic in millimeters of mercury in the three positions. Renal biopsy revealed grade 1 nephrosclerosis.

Course.—A year after the operation, the patient's blood pressure was 236 systolic and 124 diastolic in the sitting and 222 systolic and 120 diastolic in millimeters of mercury in the standing position. He worked eight hours daily for the railroad and was free of dizziness or headaches. He was short of breath on climbing stairs. Otherwise he felt fine. Two years after operation a note was received from California, stating that he had an office job and was free of symptoms. The patient's blood pressure on the right was 170 systolic and 110 diastolic in the sitting position.

Comment.—This is the case of a middle-aged man who when entering the hospital exhibited grade 1 hypertension; he showed a satisfactory drop on administration of barbiturates. However, there was evidence of arteriosclerosis in the major arteries, notably in the aorta. He had a calcified plaque near the origin of the right subclavian artery, and the aortic knob was large and calcified. Nephrosclerosis in this type of patient is moderate and progresses slowly. The operation obviously does nothing to remedy the arteriosclerosis of the major vessels. It is true that he became asymptomatic, but rest and change to an easier job would have done this for him. Having observed a small group of such arteriosclerotic hypertensive patients postoperatively, we have come to the conclusion that they are not noticeably benefited from the operation. However, attention will be called later to the redistribution of effective blood volume which occurs in all patients with complete splanchnic section and which relieves some of their symptoms; it may also be responsible for ischemic symptoms in the brain and heart, since dizziness, blindspots or relative coronary insufficiency can occur in these patients. We have placed them in this third

group of nonoperable patients, although on mechanical grading they belong to the first group. Evidence of arterial and arteriolar sclerosis of degenerative nature is the dominant feature in this group. This is not to be confused with the hyperplastic arteriolar sclerosis and productive endarteritis which is seen in some of the toxic and inflammatory renal lesions leading to hypertension.

Special Subgroups.—All classifications of hypertension contain a differentiation between a nonrenal and a renal type of hypertension. It is generally assumed that the case of the so-called neurogenic type of hypertension is the ideal case for splanchnic nerve section. In fact, an effort has been made to differentiate the neurogenic from the renal hypertension by the response of the patient's blood pressure to high spinal anesthesia, since presumably the patient with the neurogenic type would be the one to operate on.[11] In addition, Grimson and his

TABLE 9.—*Classification of Patients Suffering from "Essential" Hypertension*

Nonrenal	Number of Patients	
"Neurogenic"	3	
Endocrine	2	
Atheromatous	3	
Total number	—	8
Renal		
Unilateral renal disease	4	
Renal trauma	2	
Toxemia of pregnancy	6	
Pyelonephritis	3	
Scarlet nephritis	5	
"Rheumatic kidney"	3	
Total number	—	23
Unclassified—19		50

co-workers have proposed total sympathectomy in man because in their experimental neurogenic hypertension, produced by section of the buffer nerves, more limited procedures, such as splanchnic nerve section and dorsolumbar sympathectomy, were of little avail.[12]

Our experience, however, has not supported the view that the patients with nonrenal hypertension do better after operation than the patients with definable renal lesions. In our series an attempt has been made to define these groups, so that a comparison of results can be made between them (table 9). Naturally the extent of vascular damage,

11. Page, I. H.; Taylor, R. D.; Corcoran, A. C., and Mueller, L.: Correlation of Clinical Types with Renal Function in Arterial Hypertension: II. Effect of Spinal Anesthesia, J. A. M. A. **124**:736 (March 11) 1944. Page, I. H.: Certain Aspects of the Relationship Between Hypertension and Anesthesia, Anesth. & Analg. **22**:196, 1943.

12. Grimson, K. S.: Total Thoracic and Partial to Total Lumbar Sympathectomy and Celiac Ganglionectomy in Treatment of Hypertension, Ann. Surg. **114**:753, 1941.

as developed in the previous grading, has a potent influence with the groups.

THE RENAL BIOPSIES

The technic of performing a renal biopsy, a simple procedure which prolongs the operation by only a few minutes, has already been described. We have omitted it only in patients in whom because of severe hypotension or a large pneumothorax it was thought advisable to terminate the operation as soon as possible.

In an attempt to revascularize the ischemic kidney by omental or muscular grafts, Scupham and one of us (G. de T.) illustrated the value of cortical specimens taken from the kidney in 1940. We were stimulated to use this method of study by the excellent work of Chabanier and his co-workers,[13] who pointed out the difficulty of interpreting a late histologic picture, and to determine whether it is primarily vascular with secondary nephritic changes or primarily inflammatory with secondary vascular changes. Since 1939 we have taken sixty-five renal biopsy specimens, overwhelmingly from only one side, since with the exception of a few cases of unilateral renal disease the lesion was bilateral and differed little if at all on the two sides.

In the meantime the excellent correlation of clinical studies and renal specimens was presented by Smithwick and his co-workers.[14] They established the fact that the severer the renal vascular disease the more reduced were the glomerular filtration rate and the renal blood flow. They also found that constriction of the efferent glomerular arterioles as represented by the filtration rate was not present in the early stages of renal vascular disease. Finally they emphasized the finding that clinical hypertension and its grades of severity were ahead of the microscopic changes. In other words, hypertension semed to precede renal vascular disease, which seemed secondary to it.

Our microscopic studies, undertaken at various periods between 1939 and 1945, were made by Dr. S. R. Rosenthal, Dr. Edwin F. Hirsch and the late Dr. Richard M. Jaffé. They have been restudied and reclassified by one of us (R.J.J.). Dr. Granville R. Bennett offered

---

13. Chabanier, H.; Gaume, P., and Lobo-Onell, C.: Vue d'ensemble sur les résultats d'interventions pratiquées dans quarante-neuf cas de néphroangiosclé roses, Presse méd. **46**:1818, 1938.

14. (*a*) Castleman, B.; Smithwick, R. H., and Palmer, R. S.: Renal Biopsies from Hypertensive Patients, Am. J. Path. **17**:617, 1941. (*b*) Talbot, J. H.; Castleman, B.; Smithwick, R. H.; Melville, R. S., and Pecora, L. J.: Renal Biopsy Studies Correlated with Renal Clearance Observations in Hypertensive Patients Treated by Radical Sympathectomy, J. Clin. Investigation **22**:387, 1943. (*c*) Castleman, B., and Smithwick, R. H.: The Relation of Vascular Disease to Hypertensive State Based on Study of Renal Biopsies from One Hundred Hypertensive Patients, J. A. M. A. **121**:1256 (April 17) 1943.

valuable counsel. We have also studied the juxtaglomerular apparatus in some cases, with the help of Dr. E. D. Lambert, but have not found it to be of any help in the problems involved.

An intensive study of thirty renal biopsy specimens was made. We have used the terminology of Moritz and Oldt in describing vascular changes, recognizing subintimal hyalinization, medial hypertrophy and endothelial hyperplasia with reduplication of the internal elastic membrane. The material has been grouped into five classes similar to the scheme of Castleman and Smithwick.[14] A table of degree of changes observed follows:

Grade	Number of Biopsy Specimens	Per Cent
0	2	6.6
1	9	30
2	9	30
3	6	20
4	4	13
	30	100

The two biopsy specimens which showed no vascular changes were from 1 patient with group 1 hypertension. Glomerular structures, interstitial tissue and tubules were without change. The biopsy specimens classified as group 1 demonstrated beginning subintimal hyalinization of scattered arterioles, and occasionally vessels over 100 microns in diameter revealed slight thickening of the media, although only a few were affected. There was an occasional narrow wedge-shaped area of fibrosis, and one or two glomeruli were completely scarred (fig. 8).

In group 2 the changes were more advanced and the vessels were immediately more conspicuous. The subintimal hyalinization was prominent in the involved arterioles and was present as a thick complete collar of pink-staining material. Furthermore, in vessels over 100 microns in diameter, beginning reduplication of the internal elastic membrane was apparent. Usually more glomeruli were hyalinized and focal infiltration of round cells was seen (fig. 9).

The six biopsy specimens classified as group 3 revealed involvement of almost all vessels. The arterioles contained hyalin rings of varying thickness, and in several of the larger arterioles and smaller arteries reduplication of the elastica was prominent. In others hypertrophy of the media was present. In this group distinct narrowing of the lumens by encroachment of thickened vessel walls was clearly seen. In some, sizable wedge-shaped areas of fibrosis and cellular infiltration were present (fig. 10).

In the last group every vessel was involved and the narrowing of the lumens, observed in the previous class, had advanced to almost complete obliteration in many instances. Hyalin could be seen in many of the arterioles, but others demonstrated pronounced intimal prolifera-

tion and elastic reduplication, with narrowing of the orifices to mere slitlike openings. In 1 case necrosis of the afferent arteriole and glomerulus was observed, and this was considered as an example of so-called malignant nephrosclerosis. In these biopsy specimens the interstitial scarring was not so pronounced as that in the previous group,

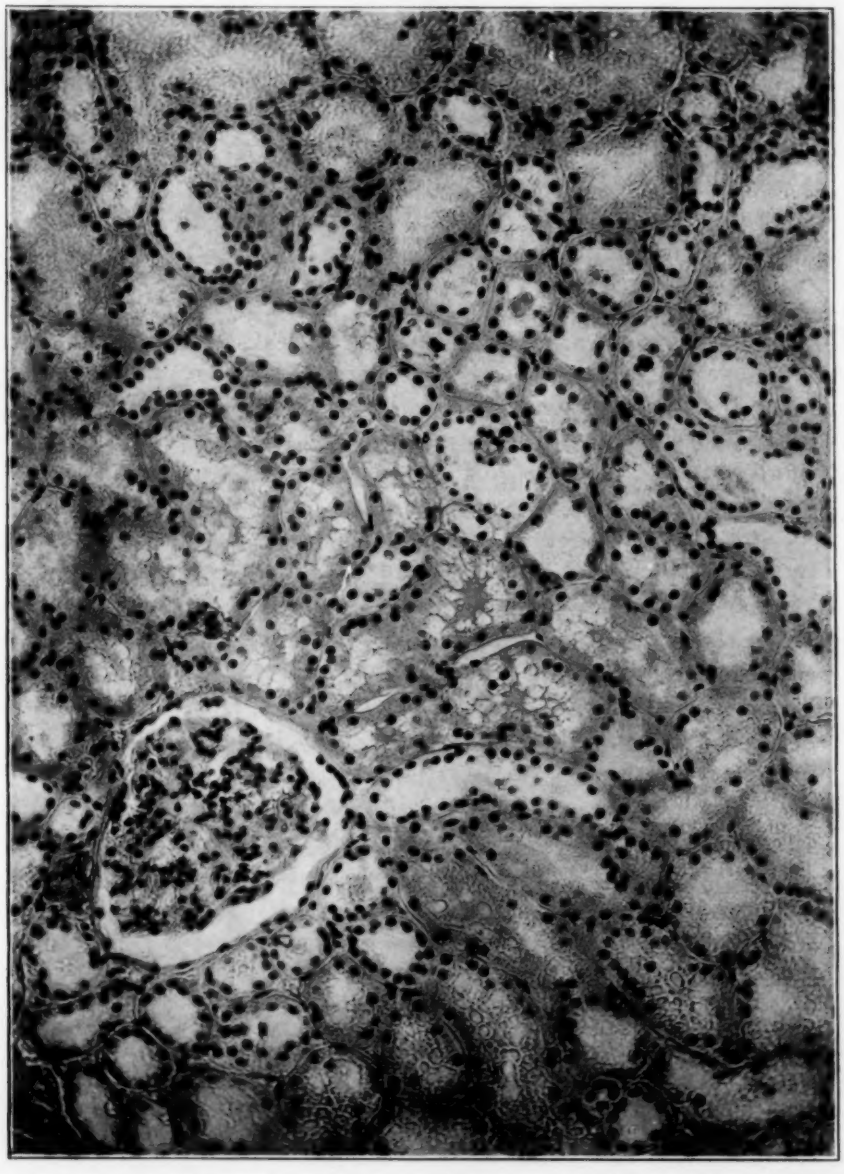


Fig. 8.—Vascular changes, group 1. There are essentially normal glomerulus and tubules. One arteriole above the tuft shows beginning hyalinization.

suggesting a more rapid tempo to the arterial and arteriolar changes (fig. 11).

From the pathologic standpoint, the first three groups constitute over 60 per cent of the cases. In these the vascular changes at most are

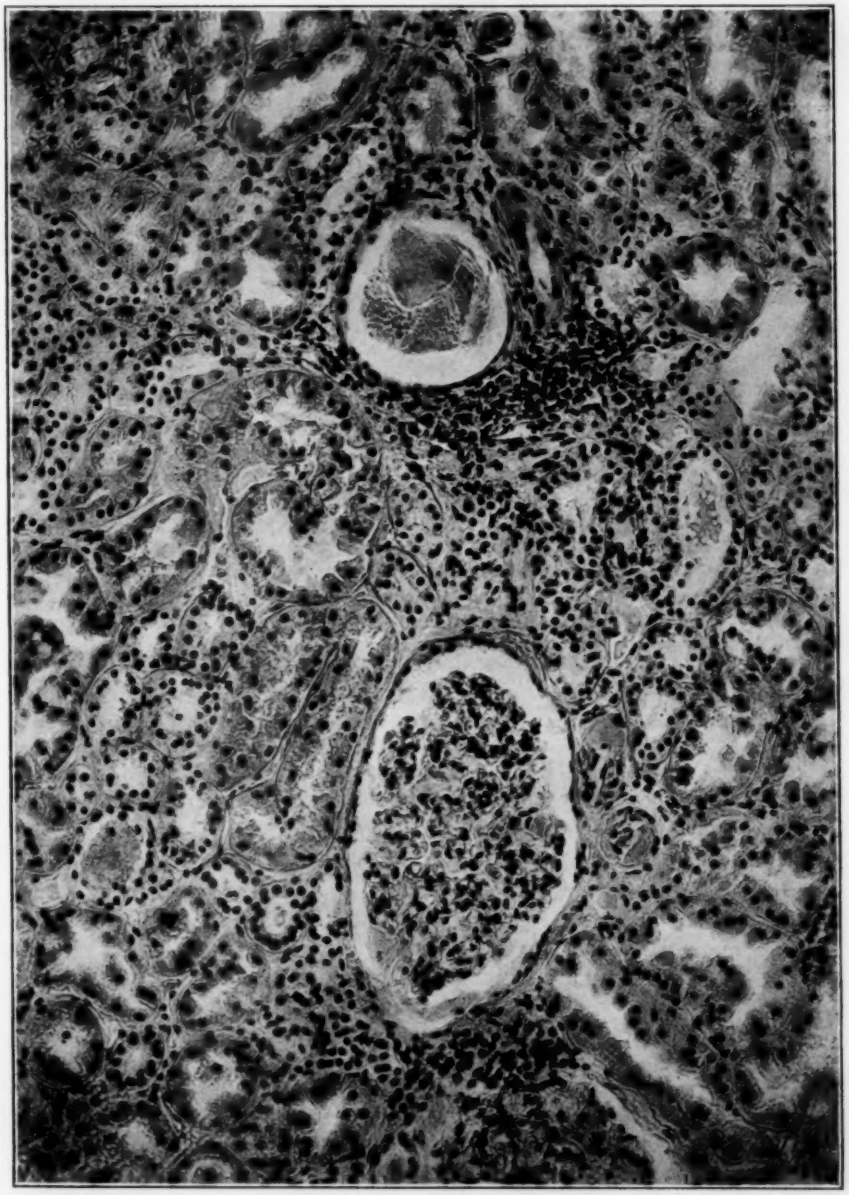


Fig. 9.—Vascular changes, group 2. Two arterioles below the glomerulus demonstrate more pronounced hyalinization. There is slight scarring and round cell infiltration of interstitial tissues.

minimal in character. Only in the latter two are the advanced changes apparent which are frequently encountered in necropsy material. Although this series is small, it is of especial interest to see that in these patients having hypertension over prolonged periods vascular changes in over 60 per cent are still within normal limits. This is further supportive evidence of the conclusion of Smithwick and Castleman that the hypertensive state antedated the vascular change.

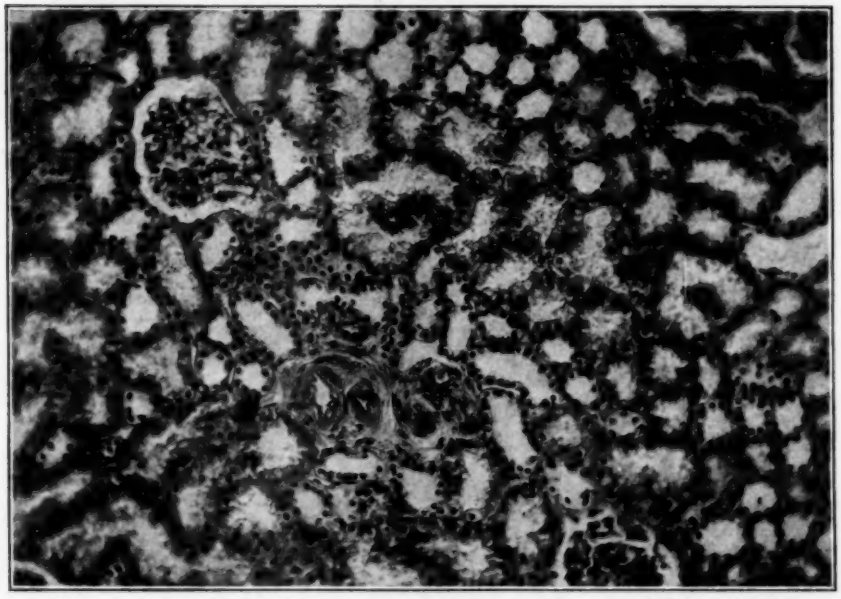


Fig. 10.—Vascular changes, group 3. The arterioles are more prominent and demonstrate subintimal hyalin and splitting of the internal elastic membrane.

The main question to be answered is, briefly, this: What information can the renal biopsy furnish toward the better understanding of the individual case? The second question is this: Does it have more prognostic value than the clinical study and the biopsies of muscle?

One of our earliest biopsies revealed chronic pyelonephritis in a young girl who gave the clinical picture of juvenile essential hypertension. Since a differential diagnosis between pyelonephritis and nephrosclerosis is important in this connection and since pathologists are more familiar with the end stages of the disease on the postmortem table, we are presenting a table based on the monograph of Weiss and Parker [15] (table 10). It will be noted that this table does not consider

15. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

the behavior of the glomeruli, tubules and interstitial tissue and is concerned only with the vascular system.

This differentiation between inflammatory and degenerative changes, however, also holds for other renal vascular lesions, such as we

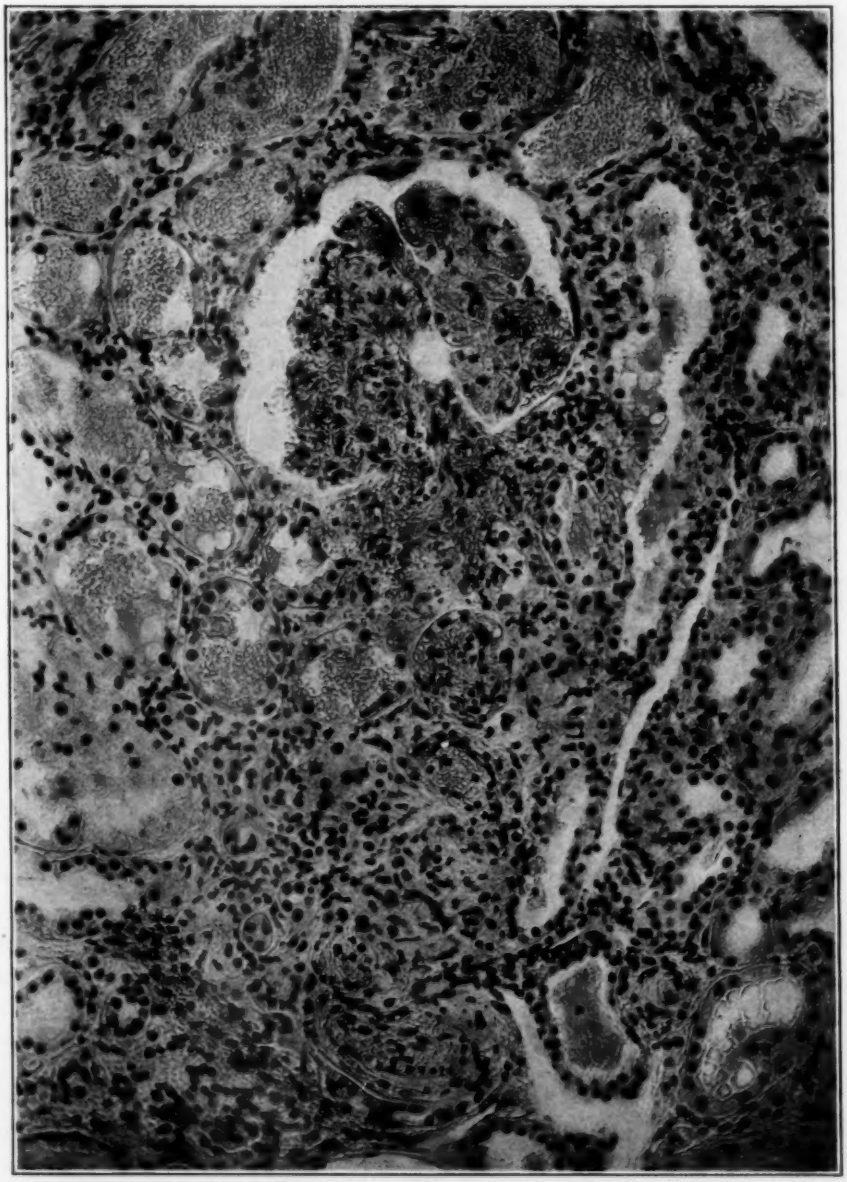


Fig. 11.—Vascular changes, group 4. The kidney in a case of malignant nephrosclerosis. There is necrosis of the tortuous afferent arteriole and the glomerular tuft.

encountered in glomerulonephritis, in streptococcic nephritis, in rheumatic lesions and in lesions accompanying Buerger's disease and panarteritis nodosa. Its significance lies in the fact that while nephrosclerosis seems to be the result of hypertension and is a secondary vascular lesion the inflammatory vascular lesions are primary in the kidney and are followed by hypertension.

Obviously, in later stages of the disease, in which nephrosclerosis is superimposed on an old inflammatory lesion, both lesions are con-

TABE 10.—*Differential Diagnosis of Vascular Lesions in Pyelonephritis and Nephrosclerosis* *

Vascular Lesion in	Pyelonephritis	Nephrosclerosis †
Arteries	Productive endarteritis (basophilic reticular tissue); reduplication of internal elastic membrane; medial hypertrophy	Internal thickening due to acidophil, dense connective tissue and hyalinization; splitting and reduplication of the internal elastic membrane
Arterioles	Concentric proliferation of cells with increase in collagen; hyperplastic arteriolar sclerosis; hyaline degeneration only in the older group	Hyaline degeneration

* Based on the monograph of Weiss, S., and Parker, F., Jr., Medicine **18**: 221, 1939.

† The malignant phase produces changes identical with those seen in pyelonephritis, i. e., productive endarteritis and hyperplastic arteriolar sclerosis.

comitantly present and it may be difficult to establish the priority of one over the other. It is also clear that different infections or toxic or allergic factors acting on the renal vascular bed will present the same proliferative reaction unless caught in the acute phase. This is equally true of the peripheral vascular bed in cases of thromboangiitis obliterans, panarteritis nodosa or rheumatic arteritis in which the characteristic picture is frequently absent when biopsies are performed during the chronic or healed stages. In our material, patients have been studied suffering from Buerger's disease, lupus erythematosus or streptococcic infections who exhibited hypertension and an inflammatory vascular reaction in the kidney without permitting a specific diagnosis.

One can state, then, that the differentiation of a primary inflammatory or secondary degenerative vascular lesion ought to be possible, especially in the earlier cases in which these biopsy specimens originate. The second problem is whether or not the renal biopsy performed during the first stage of the two stage procedure gives any prognostic help and whether it may modify the surgical procedure of the second stage. Examples of this type can be illustrated by the cases of L.T.B. and L.C.; both of these patients showed such severe renal changes and their

reaction to the first stage was so poor that the second stage was never carried out.

When an attempt was made to correlate the clinical grading with the grading of the histologic sections, as undertaken by Castleman and his co-workers,[14] their contention that the clinical grades are generally more advanced than the renal histologic changes was thoroughly substantiated. Table 11 summarizes our findings.

Another question arises regarding the comparative value of biopsies of muscle and whether or not such biopsies, performed during the preoperative work-up or during the first stage of the operation, would be

TABLE 11.—*Correlation of Clinical Grades of Hypertension with Renal Histology*

Grades	Number of Cases		Comment
	Clinical	Renal	
1	10	14	Four patients with grade 2-3 hypertension had grade 1 renal changes
2	13	9	Four patients differed, the biopsy specimens always showing less advanced changes
3	7	7	One patient with malignant hypertension had a grade 1 renal biopsy specimen; 1 grade 2 patient showed grade 3 histologic changes

an adequate substitute for renal biopsies. Heyer and Keeton,[16] from our institution, studied fifty-three specimens from skeletal muscle of hypertensive patients and concluded that regardless of the origin of the hypertension the histologic changes were the same: hypertrophy of the medial layer, constricting the lumen and altering the lumen to wall ratio. Only in the group with acute glomerulonephritis was the wall to lumen ratio slightly below that of the normal group. Once a pathologic lumen to wall ratio was established this was irreversible, since it did not change after a sympathectomy even though the pressure returned to normal. It is obvious, then, that, as first brought out by Kernohan, Anderson and Keith,[17] the hypertension can be graded and clinically correlated by the help of biopsy specimens taken from skeletal muscle. Nothing can be said, however, about the origin of hypertension, whereas the renal biopsy may here furnish more definite information.

Foa, Foa and Peet [18] stated on the basis of three hundred and fifty biopsies of muscle that they correlate well with blood pressure readings,

16. Heyer, H. E., and Keeton, R. W.: Arteriolar Changes of Skeletal Muscle in Patients with Hypertension of Varied Origin, Am. J. Clin. Path. **11**:818, 1941.

17. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395 (Sept.) 1929.

18. Foa, P. P.; Foa, N. L., and Peet, M. M.: Arteriolar Lesions in Hypertension: A Study of 350 Consecutive Cases Treated Surgically; an Estimation of the Prognostic Value of Muscle Biopsy, J. Clin. Investigation **22**:727, 1943.

changes in the eyegrounds and postoperative results. They suggest routine biopsies of muscle.

Our experience with biopsies of muscle has been that unless careful micrometer measurements are made by the same person nothing more than luminal constriction can be diagnosed; the methods of fixation and the site of the biopsy specimen may influence the wall to lumen ratio. Since we use a pedicled muscle flap to cover the renal defect, a small specimen of muscle is always obtained, more for purposes of record than for any help that it offers.

We have not been able to secure any renal biopsy specimens several months or years after splanchnic nerve section to compare them with the preoperative picture. As we pointed out in a previous communication, there was no observable change after muscle or omental transplants. While it is hard to imagine that glomeruli could be revascularized, tubular revascularization and hypertrophied tubular function which occur during the course of repair in man [19] might be facilitated. However, as will be discussed under the heading of general comment, the beneficial effect of splanchnic nerve section, at least in part, is extrarenal.

SPECIAL POSTOPERATIVE STUDIES

The purpose of dorsolumbar sympathectomy and splanchnic nerve section is to lower the blood pressure of hypertensive patients to a normal or at least a lower and more stable basal level. However, other observations can be made to substantiate the value and clarify the mechanism of such operations.

The Eyegrounds.—During our earlier studies photographs of fundi were taken at the Research and Educational Hospitals by Dr. T. Riser of all patients before and after splanchnic nerve section.[20] The regression of papilledema is striking in the group of patients with malignant hypertension, but it has no prognostic significance, since the patient still dies within the first year. The papilledema may recede even if systemic arterial blood pressure hardly falls, indicating that venous pressure and spinal fluid pressure are instrumental in its maintenance. This would fit with our conception that splanchnic section acts like an intermittent venisection, since the blood depots fill up and less of the blood volume circulates.

Papilledema and extensive retinal hemorrhages have caused us to reject the patient for operation, since they indicate malignant or pre-

19. Oliver, J.: Architecture of the Kidney in Chronic Renal Disease, New York, Paul B. Hoeber, Inc., 1939.

20. Scientific Exhibit, American Medical Association, 1942.

malignant vascular damage. Occasionally the administration of ascorbic acid and of vitamin P (hesperidin) may improve the retinal status, but the dominant factor in the production of retinal vascular sclerosis is the height and duration of arterial hypertension. The diabetic hypertensive patient has a type of venous thrombosis with secondary hemorrhage which usuallly accompanies the peripheral neuropathy of diabetic patients [21] and which seems to have no relation to high blood pressure.

Vasospastic retinopathy which is seen with or without general hypertension requires careful ophthalmologic study. The study of Gifford and Marquardt is recommended in this connection.[22]

Since the study of the retina allows a certain insight into the status of cerebral circulation, 1 patient in whom a partial amblyopia developed following operation needs special mention.

Mrs. A. R., a 50 year old woman with hypertension grade 2, had bilateral splanchnic nerve section done on Aug. 25 and Sept. 26, 1944. Her preoperative retinal study showed grade 2 arteriosclerotic retinopathy. Her preoperative blood pressure was 230 systolic and 164 diastolic to 200 systolic and 150 diastolic. On September 29, three days after the completion of the second stage, the patient complained of a kidney-shaped spot in the field of vision. It was located a short distance to the right of the fixation point. No lesion was found in the eyegrounds, although the right macula looked a bit anemic. The blood pressure was 170 systolic and 130 diastolic in millimeters of mercury. The patient was followed in the eye dispensary. Seven months after operation, her blood pressure was 180 systolic and 110 diastolic. She still had a persistent black spot in front of her right eye. This must have been due to a focal cerebral ischemia.

The Roentgenograms of the Chest, Taken at a Distance of 2 Meters.—The cardiothoracic diameter and the size and shape of the aorta were noted before and after operation. The decrease in the size of the heart may be striking, and it occurs so shortly after operation that it must be due to decrease of intracardiac tension, or, in other words, to a lessening of cardiac hypertrophy, even if blood pressure is not significantly lowered. The heart of an athlete remains enlarged long after the initial physical strain; the heart of a hypertensive patient shrinks shortly after the lowering of blood pressure (fig. 12).

The Electrocardiograms.[23]—What is true of the size of the heart after operation seems to apply to the electrocardiogram. Four pairs of electrocardiograms are shown. The first electrocardiogram in each pair represents a preoperative tracing, and the second electrocardiogram in

---

21 Rundles, R. W.: Diabetic Neuropathy, Medicine **24**:111, 1945.

22. Gifford, S. R., and Marquardt, G.: Central Angiospastic Retinopathy, Arch. Ophth. **21**:211 (Feb.) 1939.

23. Dr. G. K. Fenn described and interpreted the electrocardiograms.

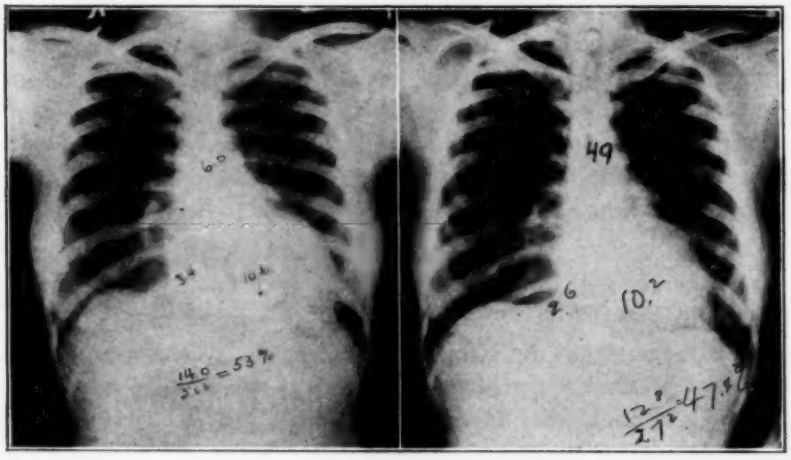


Fig. 12.—Roentgenograms of the chest taken at a distance of 2 meters before and two years after splanchnic nerve section for hypertension. Note that not only the size of the heart but the width of the large vessels has decreased.

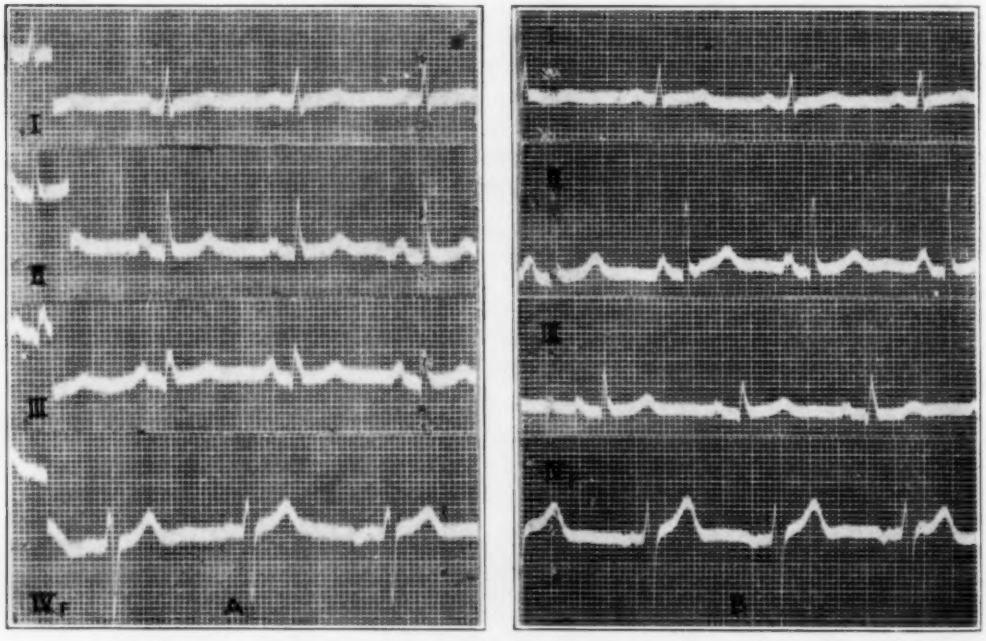


Fig. 13.—Electrocardiograms of J. F. *A*, Sept. 14, 1942, before operation, the rate was 80. The interpretation was normal rhythm with some sinus arrhythmia. The clinical diagnosis was hypertension. The tracing is not entirely normal in contour, but no diagnosis of cardiac pathologic changes can be made from this alone. *B*, Feb. 2, 1943, after operation, the rate was 75. There was sinus rhythm with a low T wave in lead I. The clinical diagnosis was hypertension. Some improvement is indicated when a comparison is made with *A*.

each pair is the last of a series of many tracings. The shortest interval between the operation and the last electrocardiogram is five months, and the longest interval is twenty-two months. In each instance the postoperative electrocardiogram shows improvement when compared with the preoperative tracing.

In the case of J. F. the improvement is minimal, but there was only slight abnormality in the preoperative curve. This is a case of grade 2 arteriosclerotic hypertension, case 8 in this series (fig. 13).

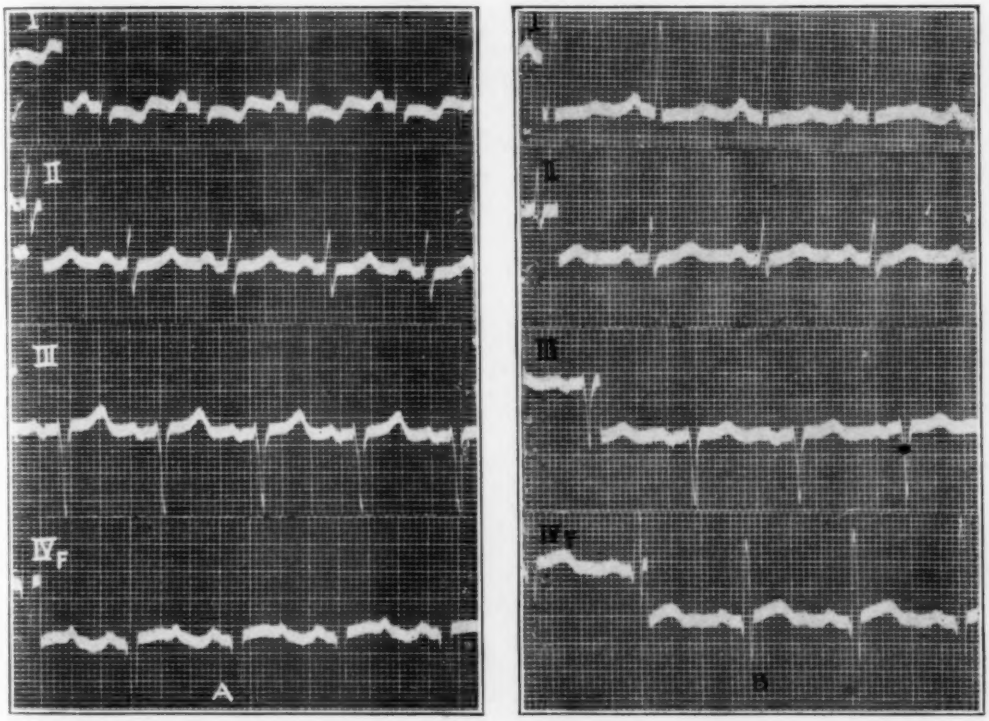


Fig. 14.—Electrocardiograms of L. R. *A*, Jan. 22, 1942, before operation, the rate was 102. The interpretation was sinus tachycardia. The T wave in lead I was inverted, and in lead IV it was diphasic. The ST segment was depressed in lead I. There was pronounced left axis deviation. This is consistent with hypertensive cardiac disease. *B*, Sept. 8, 1942, after operation, there was sinus rhythm. The T wave in lead I was diphasic, and the P wave in lead III was inverted. There was left axis deviation. Definite improvement is noted when a comparison is made with *A*.

In the case of L. R. an electrocardiogram made eight months postoperatively shows that a definitely abnormal and distorted lead 1 has been restored to a lead that shows only slight depression of the T wave. These tracings belong to a patient with severe vascular occlusion (fig. 14).

Leads I and II in the preoperative curve of J. A. are definitely abnormal, while thirteen months later they are quite normal. This occurred in case 15 (fig. 15).

The preoperative curve of J. T. is a distinctly abnormal curve in all leads except the precordial one. Twenty-two months later this curve is remarkably improved and with the exception of a moderate deformity in lead I is normal. In each case the change took place gradually (case 6, fig. 16).

It should be emphasized that the preoperative curve in each case, except that of J. F., exhibited changes that one might have assumed

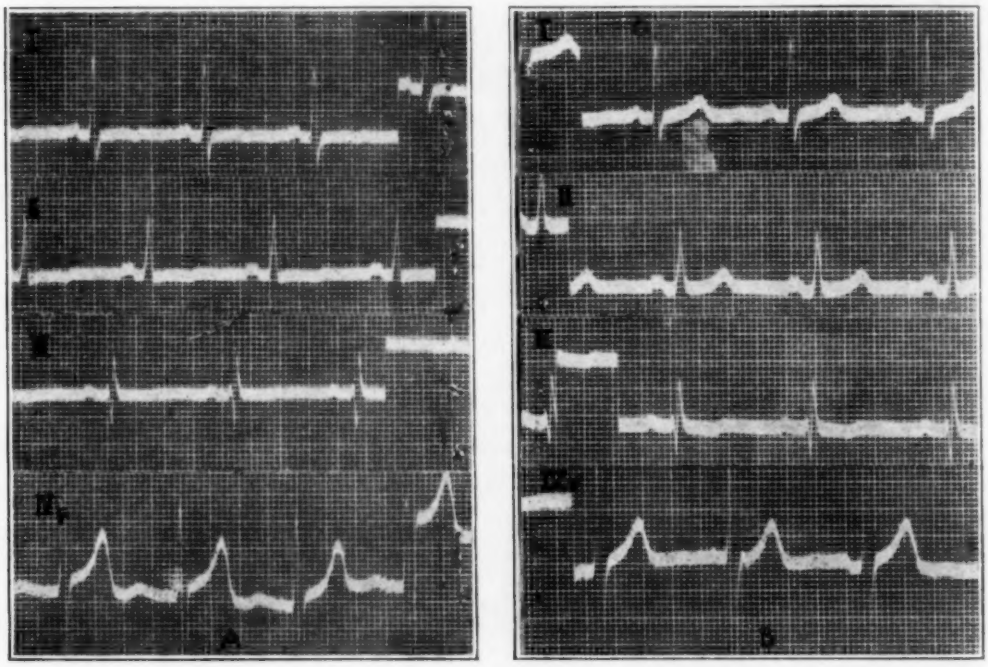


Fig. 15.—Electrocardiograms of J. A. *A*, May 20, 1943, before operation, the rate was 90. There was sinus rhythm. The T wave in leads I and II was inverted, and in lead III it was low. The ST segment was elevated in lead IV. There was evidence of myocardial damage. *B*, June 13, 1944, after operation, the rate was 70. There was sinus rhythm. The T wave in lead III was inverted. There was left axis deviation. Electrocardiographic improvement is noted when a comparison is made with *A*.

were irreversible. In each case, however, alteration began to appear that culminated in a near normal tracing.

Sensitivity to Epinephrine.—In our first paper [1] we stated that decrease of sensitivity to epinephrine was noted after splanchnic section. Generally speaking, the hypertensive patient shows an exaggerated response to epinephrine. One to 10 micrograms are injected intra-

venously, preceded by a "sham" injection of isotonic solution of sodium chloride, to test for the emotional or pain response of the patient.

It would be erroneous to believe that the "neurogenic" type of hypertensive patient is especially sensitive to epinephrine; in fact, since such patients already show some continuous vasoconstriction, their response is usually within normal limits. This is also true of animals whose buffer nerves have been removed.[24] Ominous, however, is the finding of a poor or absent response in a patient with a high diastolic pressure. This denotes—just as in the case of the cold pressor test—the continuous vasospasm of the premalignant and malignant phase and contraindicates operation.

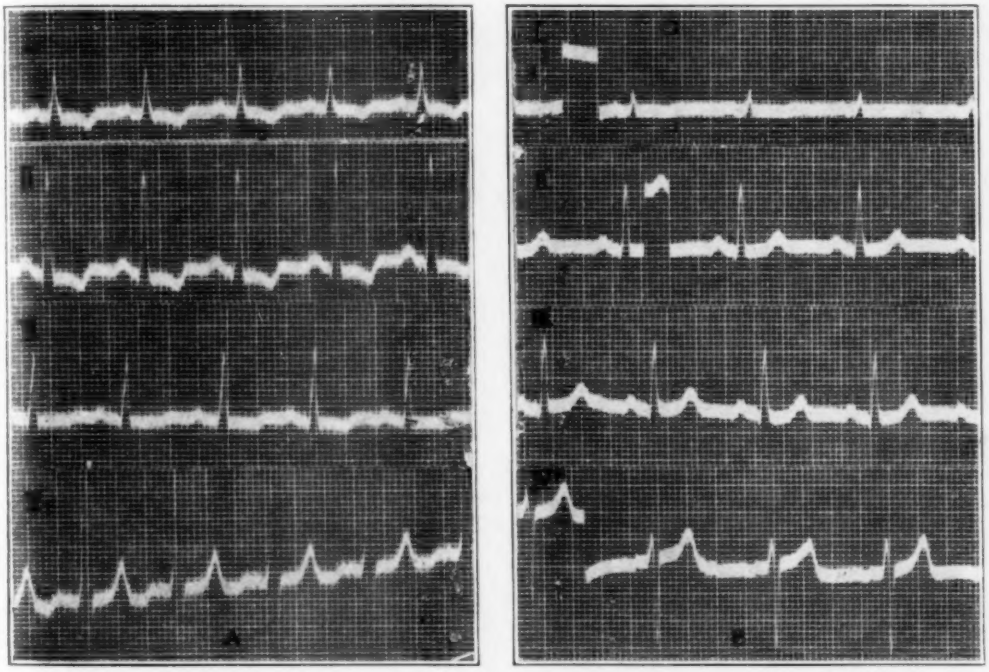


Fig. 16.—Electrocardiograms of J. T. *A*, March 19, 1942, before operation, the rate was 100. The interpretation was sinus tachycardia. The T wave in leads I, II and III was inverted. The clinical diagnosis was hypertension. There was evidence of myocardial damage. *B*, Jan. 11, 1944, after operation, the rate was 80. There was sinus rhythm. The T wave in lead I was depressed. There was moderate right axis deviation and some sinus arrhythmia. The diagnosis was hypertension. Remarkable improvement is noted when a comparison is made with *A*. Except for the moderate deformity in lead I, the curve is within normal limits.

24. Thomas, C. B., and McLean, R. L.: Effect of Intravenous Injection of Epinephrine and Angiotonin Before and After Production of Neurogenic Hypertension, Bull. Johns Hopkins Hosp. **75**:319, 1944.

The diminished response to epinephrine following splanchnic nerve section (fig. 17) is susceptible to different interpretations. It is possible that it measures a decrease of the circulating pressor substance, since the pressor substance sensitizes the blood vessels to epinephrine.[25] It might also mean that the patient after splanchnic section has lost some of his reflex nervous irritability and possibly cannot mobilize his own epinephrine so readily. Certainly patients volunteer the information that much of their "inner nervous tension," much of their emotional palpitation, is gone after operation.

While the test for epinephrine sensitivity throws an interesting sidelight on one of the mechanisms by which splanchnic nerve section acts, it has added little information to the indications for operation and its routine use has not been pursued except in certain cases.

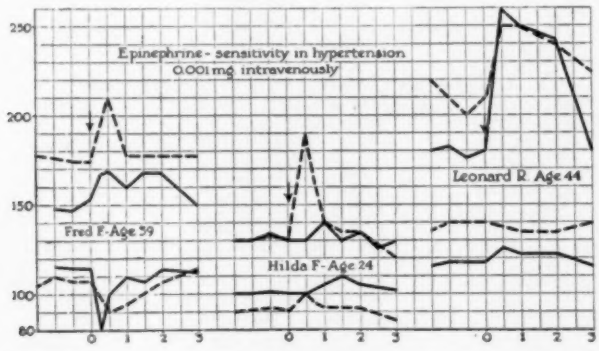


Fig. 17.—Sensitivity to epinephrine before and after splanchnic nerve section. Interrupted lines, period before operation; straight lines, period after operation. In the case of Fred F. the postoperative response was definitely diminished. Note the depressor effect of epinephrine on the diastolic pressure, which is the usual response. In the case of Hilda F. sharp systolic rise, observed before the operation, has been almost entirely eliminated. In the case of Leonard R., the postoperative response is unchanged. This patient belonged to group 3, with hypertension in a premalignant phase. While the patient derived temporary benefit from the operation, his cardiac and renal changes were advanced. He died three years after operation, from a coronary occlusion.

The Circulation Time.—When patients are tested with 3 cc. of dehydrochloric acid or with fluorescein administered intravenously, their foot to tongue circulation time varies between twenty and twenty-six seconds in the horizontal position. When the patient is standing still or on a tilting table in the upright position, this is usually lengthened to thirty to forty seconds and one draws a "blank" response more often, i. e., the patient does not experience a sudden bitter taste. After splanchnic nerve section, when the patient is in the erect position, such circu-

25. Heinbecker, P.: Role for Surgeons in Problems of Essential Hypertension, Ann. Surg. **112**:1101, 1940.

lation times which are dependent on subjective sensation are so indefinite that their use has been given up. Instead, the fluorescein given intravenously with the aid of an ultraviolet light has given more definite information. The time is greatly prolonged, indicating delayed venous return after splanchnic section, with the patient in the erect position.

Comment.—These special studies indicate that much of the vascular strain imposed on organs such as the retina, the heart and possibly the kidney is still reversible if the operation is not delayed too long. This certainly seems to be true of the size of the heart and the electrocardiogram; that the retinal circulation is spectacularly influenced has been reported early by Peet and his co-workers.[26] Most of these beneficial changes can be explained by the reduced tension in the vessels and this in turn by the diminished venous return from the splanchnic area and the lower extremities.

The decrease in sensitivity to epinephrine is an expression of adrenal denervation. Adrenal denervation, as pointed out by Heinbecker,[25] decreases reflex nervous irritability; it also seems, as he pointed out, that the renal pressor substance sensitizes the blood vessels to epinephrine. Clinically, most patients state that an "inner nervous tension" has been relieved, and this statement is being made, without direct questioning, by the illiterate farm hand, by the high tension city dweller or by the pampered only child without an occupation.

We have no evidence to present that the customary renal functional studies show any difference before and after sympathectomy, at least with the patient in the horizontal position; this is the conclusion of Talbot and his co-workers.[14b]

What has impressed us the most is the redistribution of circulation following splanchnic nerve section and its possible influence on the relief obtained. Our blood volume studies carried out with the recent modification of Gregersen[27] are not sufficiently numerous or easy enough to interpret. But the great slowing of circulation time with the patient in the erect position points to the pooling of blood in the denervated areas, with a decrease of venous return. This would account for the disappearance of headaches and dizziness, the disappearance of papilledema, the decrease in spinal fluid pressure, the decrease in the size of the heart, the improvement in the electrocardiogram and the disappearance of palpitation, all of which may occur without a notable drop

26. Peet, M. M.; Woods, W. W., and Braden, S.: The Surgical Treatment for Hypertension: Results in 350 Consecutive Cases Treated by Bilateral Supradiaphragmatic Splanchnicectomy and Lower Dorsal Sympathetic Ganglionectomy, J. A. M. A. **115**:1875 (Nov. 30) 1940.

27. Gregersen, M. I.: A Practical Method for the Determination of Blood Volume with the Dye T-1824, J. Lab. & Clin. Med. **29**:1266, 1944.

in blood pressure, which have been interpreted by Volini and Flaxman [28] as being entirely nonspecific and which could result after any operation.

It is well to regard splanchnic nerve section and dorsolumbar sympathectomy as having a vast influence on the blood depots of the splanchnic area and on those of the lower extremity. It is sufficiently known that the spleen, liver, kidney and gastrointestinal tract may hold a considerable amount of blood, and so does the subpapillary venous plexus of the skin.[29] When the patient is in the erect position, the sympathetic nervous system is the one that empties such depots.

When we deprive the hypertensive patient of his vasomotor mechanism, his adjustment to the erect posture will suffer. Starr's studies on the incoordination of circulation as determined by the response to arising [30] indicate that when the vasomotor apparatus is insufficient the cardiac output increases and should this second mechanism fail involuntary muscle spasms occur before collapse.

In examining patients shortly—up to four to six weeks—after bilateral splanchnic nerve section and dorsolumbar sympathectomy, they show the postural hypotension [2] and the postural dyspnea [31] which is characteristic of a successful denervation. However, this is compensated within a few weeks, and the postural tachycardia, which is present from the first, remains the longest. This increase in cardiac output is tolerated well by the properly selected patient, but attention should be called to patients (case 6) who show signs of coronary insufficiency for a long time. One of us (G. de T.) observed a patient who had a transdiaphragmatic sympathectomy done elsewhere and who not only had slight reduction of blood pressure but could hardly sit up or walk without becoming dyspneic; yet he had no evidence of congestive heart failure or an attack of coronary thrombosis. The surgeon must be aware, then, of the fact that splanchnic nerve section is going to throw an additional burden on the heart of the patient in the erect position and that the preoperative study of the myocardial reserve is important.

Since most blood depots can be emptied by carbon dioxide, the study of the pressor response to carbon dioxide seems a fruitful and simple method of study. Such studies are now in progress with the patients in the horizontal and erect positions, before and after operation.

---

28. Volini, I. F., and Flaxman, N.: Effect of Nonspecific Operations on Essential Hypertension, J. A. M. A. **112**:2126 (May 27) 1939.

29. Wollheim, F.: Die Blutreservoire des Menschen, Klin. Wchnschr. **12**: 12, 1933.

30. Starr, J.: Clinical Studies on the Incoordination of Circulation as Determined by the Response to Arising, J. Clin. Investigation **22**:813, 1943.

31. Bordley, J.; Goldstone, M., and Dandy, W. E.: The Treatment of Essential Hypertension by Sympathectomy, Bull. Johns Hopkins Hosp. **72**:127, 1943.

The Rate of Recurrence After Operation.—No report on the surgical treatment of cancer would fail to contain statistics on the percentage of recurrence after certain periods. We have studied our material from this aspect. Recurrence was defined as return of the diastolic pressure to the preoperative level. This may seem to be an arbitrary and rather lax definition, but it must be remembered that even when preoperative levels are reached the dynamics of circulation have been changed and that the life of the patient may be prolonged by diminished stress on some of the supradiaphragmatic structures.

Table 12 shows the number of recurrences among 41 patients of groups 1 and 2, since all patients belonging to the third group died within a year. Of the 8 patients with recurrence 2 belonged to the first group and both needed reoperation, after which their pressures fell. Of the second group, the 6 patients whose diastolic pressures rose to the preoperative level were carefully scrutinized. It is primarily due to these recurrences that we refuse to operate on patients who either have a

TABLE 12.—*Recurrence of Hypertension After Splanchnic Nerve Section in Fifty-One Cases Observed from 1940-1943*

Group	Total Number	Number of Recurrences *	Probable Causes
1	17	2	Both patients had incomplete operations; pressure fell after reoperations
2	24	6	Atheromatosis of large vessels or early malignant phase
3	10	All died	

* Recurrence: rise of diastolic pressure to preoperative level.

striking enlargement and rigidity of the aorta or exhibit the continuous vasospasm of severe benign nephrosclerosis or pyelonephritis, which we regard as the premalignant phase.

This table is a strong argument for operating on the patients in the first group, since with the exception of 2 patients who had technically incomplete operations all showed improvement or complete return to normal. The group of 17 patients will have to be followed for the next ten to twenty years for the final appraisal of the value of sympathectomy to hypertensive patients.

GENERAL COMMENT

Since detailed comments were made under the various headings, we simply wish to reemphasize here our present attitude toward this operation. If surgeons are really going to face this issue squarely, they must urge an early operation on all patients with group 1 hypertension whose diastolic pressures exceed 90 mm. of mercury. These patients are overwhelmingly asymptomatic and are recognized at preemployment, prein-

duction or insurance examinations. A distinction should be made between the hypertension of these patients and the hypertension of adolescents, who may come from hypertensive families and who during their period of growth and possibly increased pluriglandular function show a higher than normal pressure which may become normal in early adult life. We are watching such a boy of 15 and may have to operate on him if his pressure does not come back to normal. Lawrence [32] found 9.5 per cent of 220 students to show abnormally elevated pressures and gained the impression that most of them came from hypertensive families, that their cold pressor response was frequently abnormal and that they were in a prehypertensive stage. For this group we advise frequent reexaminations, at three month intervals. No type of medical treatment seems effective to prevent the full-blown appearance of juvenile hypertension.

Another group of patients who should be strictly separated from early juvenile hypertensive patients are those with transient nervous hypertension. Rogers and Palmer [33] found in examining 1,574 applicants studied at the Office of Naval Procurement in Boston that 14 per cent of them showed a short, transient hypertension with a normal cold pressor response. They felt that their prognosis is excellent, and in just how many of them persistent hypertension will develop is unknown.

We postulate, then, a persistent casual hypertension [34] of over 140 systolic and 90 diastolic in persons between 18 and 25 before we consider them for operation. By a casual blood pressure, we mean that it is recorded during the course of normal activity, during the day. That their basal blood pressure after bed rest, during sleep or under the influence of sedatives goes down to normal and puts them in the first group should not lull the physician into a false sense of security. It is in this group with no or minimal organic changes that our best results are obtained.

The experienced internist knows that the prognosis of these juvenile hypertensive patients is unfavorable. While the rate of progress is unpredictable, the middle-aged hypertensive patient will begin to show enough symptoms and organic damage so that he is more apt to be referred for operation. He can derive benefit if he fulfils our requirements for the second group, but some organic damage must remain. Whether his life has been prolonged is a matter for long term statistics to show. The subjective improvement, which in our opinion is due to a

32. Lawrence, H. E.: The Blood-Pressure of Adolescents, New England J. Med. **228**:381, 1943.

33. Rogers, W. F., and Palmer, R. S.: Transient Nervous Hypertension as a Military Risk, New England J. Med. **230**:39, 1944.

34. Alam, G., and Smirk, F. M.: Casual and Basal Blood-Pressures: I. In British and Egyptian Men, Brit. Heart J. **5**:152, 1943.

redistribution of the circulating blood volume and which has lasted in our material for three to five years, is in itself an important consideration and takes the place of small repeated venisections. In fact, if a small venisection does not bring about subjective improvement or a fall in blood pressure, splanchnic nerve section may prove to be useless.

The surgeon need not consider the patients in the premalignant or malignant phase, since there is no benefit to be derived from a surgical procedure. The argument is frequently brought forward that all other types of treatment have failed and that the patient has nothing to lose since his prognosis is so poor. We feel that it is useless and unfair to put a patient through a large, two stage operation, since we have never seen any benefit at this stage. Occasional spectacular results as reported in the literature may be due to nephritic exacerbation and remission of chronic benign nephrosclerosis, and patients with such results should not be classified as belonging to the group of patients with malignant hypertension.

Another conclusion which our observations justify is rather startling. Considerable effort has been spent by investigators to separate the "neurogenic" from the renal type of hypertension. Page and his group advanced the use of high spinal anesthesia and felt that the "neurogenic" group shows a considerable fall in blood pressure as contrasted with the renal group.[11] This has certainly not been our experience; in operating on a large number of older arteriosclerotic patients with hypertension under spinal anesthesia, we have repeatedly observed a severe fall in blood pressure; yet they could hardly be regarded as suitable for sympathectomy. Grimson and his co-workers produced neurogenic hypertension in dogs and found that nothing short of a total sympathectomy would abolish such hypertension.[12] For this reason they reject splanchnic nerve section as being only a partial sympathectomy; when their method is used the compensatory tachycardia which develops in the erect posture is inhibited, and this in our opinion produces an even greater incoordination of circulation than splanchnic section, since it deprives the patient from increasing his cardiac output.

In our material it is the renal group which has shown the best clinical results from splanchnic nerve section. As pointed out elsewhere,[35] patients with pyelonephritis, post-toxemic hypertension, streptococcic nephritis and rheumatic renovascular damage are favorable candidates provided the vascular lesion is not too far advanced. On the other hand, the "neurogenic" group has not done well. The fluctuations of their pressures have not been abolished, and their emotional "hypothalamic"

35. de Takats, G., and Fowler, E. F.: The Surgical Treatment of Hypertension: III. Neurogenic Versus Renal Hypertension from the Standpoint of Operability, to be published.

outbursts are not eliminated and continue to operate on the vascular system. The explanation for this phenomenon is far from being clear. It may be, as Grimson feels, that more of the sympathetic nervous system has to be removed in this group of patients.[12] However, a few of our total sympathectomies which were done in several stages have not shown any improvement over the transdiaphragmatic approach. We are more impressed with the possibility that the "neurogenic" hypertension may operate through a pluriglandular mechanism and is not mediated by the splanchnic nerves at all.

It is well established that the posterior lobe of the pituitary is readily activated by nervous stimulation and that indeed it completely atrophies if the pituitary stalk is sectioned.[36] It also seems established that when the stalk is sectioned in man, as occurred in Dandy's case,[37] a low blood pressure develops in addition to the diabetes insipidus. To round out the argument, the clinical studies of Griffith[38] should be cited, who found in a certain small percentage of hypertensive patients that their serum contains an excess of the antidiuretic hormone. The test is simple; only 1 cc. of the patient's serum is needed; this is injected intraperitoneally into rats, and their water-retaining ability is studied. In hypertensive patients with positive tests for the antidiuretic hormone of the pituitary, Prendergrass, Hodes and Griffith[39] advocated radiation of the pituitary gland. A total dose of approximately 1,000 r must be delivered, and the reaction to the test for the antidiuretic hormone must become negative. They also stated that if the response to the radiation fails in regard to blood pressure and to the test the majority of such patients have positive tests for gonadotropic hormones and should be treated by diethyl stilbestrol or testosterone respectively. In such patients hypersecretion from the posterior lobe is secondary to hypersecretion from the anterior lobe.

We are unable to verify or disprove this contention at present, but the point of a pluriglandular type of hypertension, governed by the pituitary and activated by a nervous mechanism, has much in its favor.

---

36. Fulton, J. F.: The Physiology of the Nervous System, ed. 2, London, Oxford University Press, 1943.

37. Dandy, W. E.: Section of the Human Hypophysial Stalk: Its Relation to Diabetes Insipidus and Hypophysial Function, J. A. M. A. **114**:312 (Jan. 27) 1940.

38. Griffith, J. Q., Jr.; Corbet, H. O.; Roberts, E., and Lindauer, M. A.: Studies of Criteria for Classification of Arterial Hypertension: V. Types of Hypertension Associated with the Presence of Posterior Pituitary Substance, Am. Heart J. **21**:77, 1941.

39. Prendergrass, E. R.; Hodes, P. J., and Griffith, J. Q., Jr.: Irradiation of the Pituitary Gland in Posterior Lobe Hyperfunction Controlled by Biologic Tests, Am. J. Roentgenol. **46**:673. 1941.

Such patients will not respond to splanchnic nerve section, and a simple clearcut biologic test would be most welcome to separate them from the operable patients.

SUMMARY

The surgical treatment of hypertension, based on the preoperative and postoperative study of 52 patients, is discussed in detail. For an improvement in results a rigid selection of cases is advocated. A group representing a clearcut indication is separated from one in which the indication is relative and is debatable. A third group, consisting of the patients with premalignant and malignant hypertension, is not regarded as being suitable for operation. The criteria for establishing the group with premalignant hypertension are defined. Some of the problems of anesthesia, especially the avoidance of accumulation of carbon dioxide, are discussed. The surgical procedure is described step by step, with illustrations. The transdiaphragmatic approach, to which a unilateral renal biopsy is added, has been employed in this series. The follow-up system is described, on the basis of which the results are tabulated in the three groups. In the 17 patients in group 1, the response was most gratifying. Only 2 had recurrent hypertension, which was corrected after completion of a technically incomplete operation. Six patients showed recurrence in the second group; these were analyzed and reasons found for the organic, irreversible lesions, which can be detected preoperatively. No results were obtained in the third group of patients.

The value of renal biopsies was discussed and also the help that special postoperative studies relating to eyegrounds, roentgenograms of the chest taken at a distance of 2 meters, electrocardiograms, epinephrine sensitivity and circulation times offer. The redistribution of circulation through the effect of splanchnic nerve section on blood depots has been stressed. This field offers vast opportunities for future study. So far no single or combined method of treatment can be recognized which would give rigidly selected patients with hypertension as much benefit as the transdiaphragmatic splanchnic nerve section combined with dorsolumbar sympathetic ganglionectomy.

FRACTURES OF THE CARPAL SCAPHOID BONE

An Analysis of Sixty-Six Cases

LIEUTENANT COLONEL MOSS M. BANNERMAN
MEDICAL CORPS, ARMY OF THE UNITED STATES

THE CORRECT treatment of fractures of the carpal scaphoid bone which are diagnosed early is adequate prolonged fixation. This treatment has long been recognized, but in spite of this realization a large percentage of fractures go undiagnosed and therefore untreated. This delay in diagnosis is conducive to nonunion and arthritic changes, which increase the difficulty of treatment and make results ungratifying. Mildness of symptomatology often causes procrastination of the patient in seeking medical advice. The relative infrequency of fractures of the carpal scaphoid bone in civil life makes it difficult to collect and evaluate sufficient cases to arrive at the type of treatment needed for these fractures, particularly cases in which there has been considerable delay in seeking attention.

In the armed forces, with careful medical supervision of a large group of young adults, an increasing number of fractures of the carpal scaphoid bone have been diagnosed. The series of 66 cases reported in this paper was seen over a period of two years at Harmon General Hospital and LaGarde General Hospital, constituting 5 per cent of all fractures seen during this time.

The exacting and prolonged physical demands of military training are such that fractures of the carpal scaphoid bone produce pronounced disability and result in prolonged morbidity. Military service also brings to light old undiagnosed fractures with nonunion which were incurred prior to the patients' entrance into service. In this study 8 cases of this type were seen, but they have not been included in the series.

In spite of the wide availability of x-ray facilities and the knowledge of these factors, early diagnosis is not the rule. This is immediately apparent in the table.

FACTORS IN DIAGNOSIS

In this series 42 per cent of the fractures of the carpal scaphoid bone were not diagnosed at the time of injury. Five patients, or 7 per cent, failed to report the injury for several weeks after its incurrence. In 35 per cent of this series either the fractures were diagnosed as sprains and not examined roentgenologically or the roentgenograms

From the Orthopedic Section, Harmon General Hospital, Longview, Texas.

were reported negative for fracture and the diagnosis missed. Because of these missed diagnoses, the convalescence was unduly prolonged and invaluable weeks and months of time lost to the soldier.

Healing Time for Fractures of the Scaphoid Bone

Elapsed Time Until Diagnosis, Days	No. of Cases	Roentgenograms at Time of Injury			Duration of Treatment, Mo.	Nonunion
		Positive	Negative	None		
1-30	38	36	2	0	3.7	0
30-60	5	0	2	3	4.3	0
60-120	5	0	1	4	5.1	0
120-180	6	..	2	4	5.5	0
Over 180	12	..	3	9	7.5	10
Totals.....	66	36	10	20		10

Fig. 1.—Fresh fracture of the carpal scaphoid bone. Note that the fracture is seen in only one oblique view.

Such a large number of missed diagnoses shows that one must be on the alert for fractures of the carpal scaphoid bone to make an early diagnosis. In cases in which pain and swelling of the wrist persist,

and especially when the pain and tenderness are in the region of the anatomic snuffbox, careful reevaluation and reexamination of the wrist are indicated.

Because of the large number of negative roentgenograms, it is our belief that all cases of injury to the wrist should have, in addition to the routine anteroposterior and lateral views, semilateral roentgenograms at approximately 30 and 60 degree angles. ,With the foregoing procedure, in only 2 cases were fractures of the carpal scaphoid bone not diagnosed at the time seen, and in these 2 diagnoses were made on reexamination, three weeks later (fig. 1).

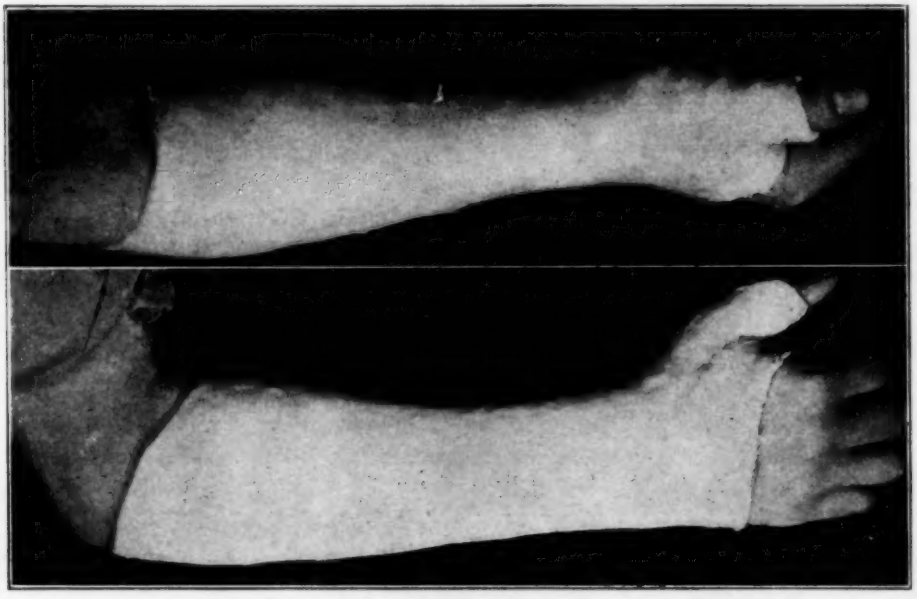


Fig. 2.—Cast for immobilization, incorporating thumb to distal end of proximal phalanx.

SYMPTOMS

The clinical picture is well known and has been adequately discussed by Soto-Hall and Haldeman.[1] In older fractures the persistent pain in the anatomic snuffbox is a constant finding, with weakness and pain after exertion. Swelling and moderate limitation of motion are less constant, but the presence of any of these conditions is sufficient to warrant detailed examination of the wrist.

1. Soto-Hall, R., and Haldeman, K. O.: The Treatment of Fractures of the Carpal Scaphoid, J. Bone & Joint Surg. **16**:822-828, 1934.

TREATMENT

Complete and prolonged immobilization is the accepted treatment in all cases. Even ten months after injury fractures which have not been treated warrant a trial of immobilization, as 15 per cent or more will give satisfactory results from this treatment alone.

Reduction of fractures of the carpal scaphoid bone is seldom necessary. When seen in association with dislocation of the semilunar bone, the fragments of the carpal scaphoid bone are usually in good position after the semilunar bone has been reduced. In this series, there are 2 cases of this type.

Immobilization by a skin-tight cast involving the thumb and extending from the elbow to the distal palmar crease was the method used. The wrist was held in moderate dorsiflexion and slight radial deviation.

Fig. 3.—Delayed union of the carpal scaphoid bone. *A*, original picture, four months after injury. *B*, three months later, showing beginning of union and aseptic necrosis of proximal fragment. *C*, after six months of treatment. Complete union is present. Revascularization is practically complete.

The thumb, held in abduction and extension, was included to the distal phalanx (fig. 2).

Casts were changed when they became loose due to atrophy of the forearm muscles. This atrophy is minimized by use of the fingers during immobilization. Check roentgenograms in all positions were taken every six weeks and immobilization continued until the fracture line completely disappeared. Inclusion of the thumb is essential for two reasons. First, the fragments are thus held in most intimate contact. Second, complete immobilization cannot be accomplished unless this is done. Union rarely occurs when the thumb is not included.

COMMENT

In 56 cases, or 85 per cent of the series, the fracture healed, without arthritic changes, by prolonged immobilization. In the oldest to heal, it had been nine months from the time of injury to instigation of immobilization. This treatment appears worthy of trial in all fractures under ten months old. In our series all fractures under six months healed satisfactorily. The presence of osteoporosis of the carpal scaphoid bone due to trauma (Preiser's disease) was no bar to healing in the 6 cases seen. Immobilization was continued until complete revascularization occurred. This was evidenced by gradual decrease of sclerosis of the fragment and restoration of uniform density as seen by the roentgenogram (fig. 3).

Operative intervention was not instituted until after at least two months of immobilization the fracture failed to show improvement. Operative treatment was performed in 10 cases. Six fractures healed with good results. In 2 cases of fracture showing pronounced arthritic changes the distal fragment was removed, with 50 per cent good results.

After immobilization in both operative and nonoperative cases, recovery of function was surprisingly rapid. All patients regained full motion and strength after only one month of use and physical therapy. This was in a great part due to the continuous use of the fingers by physical and occupational therapy during the immobilization period, in spite of the fact that these fractures were immobilized six to eight months.

CONCLUSIONS

1. In 85 per cent, or 56, of a series of 66 cases fractures of the carpal scaphoid bone seen within twelve months after injury healed by prolonged immobilization in a skin-tight cast, including the thumb. All fractures less than six months old healed by this method.

2. Diagnosis at time of injury is possible in most cases provided the surgeon is aware of the fracture and makes multiple views of the wrist at the time of injury, repeating these views if symptoms persist and when checking union. These views are discussed in detail.

PERICORONARY NEURECTOMY IN ABOLISHING ANGINAL PAIN IN CORONARY DISEASE

An Experimental Evaluation

MERCIER FAUTEUX, M.D., F.R.C.S.(C)
AND
ORVAR SWENSON, M.D.
BOSTON

A SURGICAL procedure to be of optimum value in the treatment of coronary disease must simultaneously improve the coronary circulation, block vasomotor reactions and eradicate anginal pains.[1] Operations now in use cannot achieve full benefit for the patient with coronary disease, as their specific objective is limited either to the interruption of nerve pathways that may carry pain impulses or to the improvement of the coronary circulation.

Cervical or dorsal sympathectomy may interrupt some impulses originating from the coronary vessels or the myocardium; yet it is not satisfactorily demonstrated experimentally that all important pathways carrying impulses to and from the coronary arteries are cut or that an improvement in coronary circulation follows. Cutler [2] stated, "My own experience in this field comprises a considerable number of surgical attacks on the sympathetic apparatus in the neck and on the upper two dorsal ganglia. I have never been convinced that the relief afforded by such a procedure was complete or lasting." More recently, Willius [3] wrote that "cervical sympathectomy and its various modifications as well as paravertebral injections of procaine hydrochloride and absolute

This work was aided by a grant from the Dazian Foundation for Medical Research and a grant from the Milton Fund.

From the Laboratory of Surgical Research, Harvard Medical School and the Surgical Service of the Peter Bent Brigham Hospital.

1. (*a*) Fauteux, M.: Positions actuelles du traitement chirurgical de l'angine de poitrine, Union méd. du Canada **69**:829, 1940; (*b*) Études experimentales sur le traitement chirurgical des coronarites, ibid. **72**:1260, 1943; (*c*) La neurectomie péricoronarienne associée à la ligature de la grande veine coronaire dans le traitement de certaines formes de la maladie coronarienne, ibid. **74**:424, 1945; (*d*) Treatment of Coronary Disease with Angina by Pericoronary Neurectomy Combined with Ligation of the Great Cardiac Vein, Am. Heart J. **31**:260, 1946.

2. Cutler, E. C.: The Surgical Treatment of Pain, New England J. Med. **218**:422, 1938.

3. Willius, F. A.: Coronary Disease: Certain Significant Contributions Made During the Last Quarter Century, Minnesota Med. **26**:33, 1943.

alcohol . : . have gradually but hopefully lost their appeal." On the other hand, methods proposed to revascularize the heart, which, according to their advocates, increase efficiently the blood supply to myocardial tissues, are not designed to eliminate reflexes originating from diseased coronary arteries which can lead to vascular spasms, pain and primary ventricular fibrillation.

For these reasons, it appeared to one of us (M. F.) some years ago that it would be highly advantageous to devise an operation which would simultaneously accelerate the development in size of the natural coronary anastomosis and block the reflexes concerned with coronary vasomotor disturbances, such as primary ventricular fibrillation and sudden death. Such a procedure should also eradicate anginal pains.

Since it was known through experimental and clinical evidence of other investigators that venous ligation does aid in opening and dilating the arterial anastomosis of the extremities to the extent that gangrene can be avoided in many instances of arterial occlusion, it was thought that coronary venous ligation could help substantially to realize the first objective. Experimental [4] and clinical [5] evidence seems to support this view. It was also assumed that the procedure described by one of us (M. F.) under the name of pericoronary neurectomy could be of great value in achievement of the second objective.

Extensive experimental studies were carried out by one of us (M. F.). The results obtained show unquestionably the respective value of the two procedures as well as their respective limitations. It may be of interest to summarize briefly certain facts concerning the results acquired in these experiments.[6] In one group of dogs, used as a control series, the circumflex artery was ligated at its origin. Twenty per cent of the animals survived. In a second group, prepared in advance by coronary venous ligation alone, the circumflex artery was ligated as in group 1. Fifty per cent of the dogs survived. It is interesting to note that most of the animals lost died soon after the arterial occlusion, apparently due to primary ventricular fibrillation. In a third group, prepared in advance by pericoronary neurectomy alone, ligation of the circumflex artery was done as in the previous group. Sixty per cent of the animals lived. Another interesting point to note is that most of the dogs that died suc-

---

4. (*a*) Gross, L.; Blum, L., and Silverman, G.: Experimental Attempts to Increase the Blood Supply to the Dog's Heart by Means of Coronary Sinus Occlusion, J. Exper. Med. **65**:91, 1937. (*b*) Fauteux, M.: Experimental Study of the Surgical Treatment of Coronary Disease, Surg., Gynec. & Obst. **71**:151, 1940.

5. Fauteux, M., and Palmer, J. H.: Treatment of Angina Pectoris of Atheromatous Origin by Ligation of the Great Cardiac Vein, Canad. M. A. J. **45**:295, 1941.

6. These experimental studies are to be reported in detail and discussed in a monograph which is in preparation.

cumbed much later than those of the group with venous ligations. Apparently they died of cardiac failure due to cardiac ischemia. In a fourth group, prepared in advance by pericoronary neurectomy and coronary

Fig. 1.—Section of a nerve resected from the heart of a dog during pericoronary neurectomy.

venous ligation, the circumflex artery was again tied, as in the other groups. The survival rate rose to 86 per cent.

The following conclusions were reached regarding these two procedures. Coronary venous ligation helps to open and dilate the coronary

anastomotic branches and consequently encourages collateral circulation. The postoperative course in a series of patients who had ligation of the great cardiac vein alone shows the beneficial effect of this operation. All these patients, who were unable to work before operation, have returned to work. In 3 cases five years have elapsed since the ligation of the great cardiac vein, and in 4 cases four years have elapsed since operation. The fact that the patency of the newly opened coronary anastomosis is not only an immediate and temporary effect has been demonstrated elsewhere.[1d] Yet it is obvious that this procedure does not prevent the initiation of reflexes and, therefore, does not seem to diminish the incidence of primary ventricular fibrillation. This is in accordance with the results obtained by other investigators.[7] It does not mean, however, that coronary venous ligation has no therapeutic value. Applied to the heart, the beneficial action of venous occlusion is often masked by deleterious reflexes which rapidly follow after sudden coronary occlusion. When the reflexes are blocked, the value of this measure appears more clearly. This is shown by the results obtained in the fourth group and in the group of Beck and Mako, in which ligation of the great cardiac vein was combined with a partial arterial occlusion, which to a certain extent prevents deletrious reflexes.

That pericoronary neurectomy definitely aids in prevention of primary ventricular fibrillation and rapid death after coronary ligation is well demonstrated by the results obtained in group III. It apparently also helps to improve collateral circulatory conditions by abolishing reflexes interfering with the coronary anastomotic system. Alone, however, it does not suffice to prevent cardiac ischemia or secondary death in every instance. When the two procedures are combined at the same operation, the importance and value of their association appear clearly.

One important point that remained unsolved by these experiments is to what extent this type of operation could diminish the incidence of pain in coronary disease. This question is studied in the present report.

The experimental method for studying cardiac pain responses, although not beyond criticism, has been fairly well standardized. It was described and used by Sutton and Lueth.[8] The procedure is as follows: With the animal under ether anesthesia, without the use of morphine or other sedative and with artificial respiration, the chest was opened in the fifth left intercostal space, the parietal peri-

7. Beck, C. S.: Natural and Artificial Collateral Circulation in the Heart, in Blood, Heart, and Circulation: A Symposium, American Association for the Advancement of Science, Washington, D. C., 1940, p. 133. Beck, C. S., and Mako, A. E.: Venous Stasis in the Coronary Circulation: An Experimental Study, Am. Heart J. **21**:767, 1941. Gross, Blum and Silverman.[4a]

8. Sutton, D. C., and Lueth, H. C.: Pain: Experimental Production of Pain on Excitation of the Heart and Great Vessels, Arch. Int. Med. **45**:827 (June) 1930.

cardium being exposed. Through a small incision in the parietal pericardium, a ligature was passed around the ramus descendens of the left coronary artery, without being tied. This ligature was passed through a flanged glass tube, which led the ligature to the surface. A purse string suture closed the pericardial incision and at the same time included the flange of the glass tube, thus fixing the tube in place. The proximal end of the tube was sutured in the wall of the chest, and the incision was closed, care being taken to remove any pneumothorax. After three or four hours, when the animal had completely recovered from the anesthesia, was active and showed little shock from the operation and apparently no pain, the cardiac pain test was carried out. By fixation of the external portion of the glass tube and traction on the ligature, the artery can be temporarily occluded. The signs demonstrating pain in the dog, according to Sutton and Lueth, were restlessness, rigidity of the left foreleg, changes in the amplitude and rate of the respirations, nausea, salivation, vomiting and whining. Katz, Mayne and Weinstein [9] and White, Garrey and Atkins,[10] who carried out similar tests in dogs, described identical signs. Sutton and Lueth considered that the pain response is due solely to the interference with the coronary blood flow and not to any adventitious factors incidental to the procedure itself. Katz, Mayne and Weinstein expressed the opinion that the positive response is due to compression of afferent fibers enclosed within the sheaths of the coronary vessels and not to occlusion of the coronary artery by the ligature and the consequent change in the flow of the blood. This test has been considered accurate enough to be used as a means of evaluating the effectiveness of various surgical procedures to interrupt the sensory pathways of the heart.[11]

EXPERIMENTAL STUDIES

In the present investigation, the procedure used was similar to that described by Sutton and Lueth. The pain reaction was studied in 20 dogs, divided into two groups of 10 animals each.

Group I (Control Group).—The animals were anesthetized with intratracheal ether under positive pressure. The heart was exposed through a

9. Katz, L. N.; Mayne, W., and Weinstein, W.: Cardiac Pain: Presence of Pain Fibers in the Nerve Plexus Surrounding the Coronary Vessels, Arch. Int. Med. **55**:760 (May) 1935.

10. White, J. C.; Garrey, W. E., and Atkins, J. A.: Cardiac Innervation, Arch. Surg. **26**:765 (May) 1933.

11. White, J. C.: Experimental and Clinical Studies in the Surgical Treatment of Angina Pectoris, Ann. Int. Med. **7**:229 (Aug.) 1933. Cutler, E. C., and Shambaugh, P.: Total Thyroidectomy in Angina Pectoris, Am. Heart J. **10**:221, 1934. Moore, R. M., and Singleton, A. O.: Peripheral Course of Pain-fibers Supplying Coronary Arteries and the Myocardium, Proc. Soc. Exper. Biol. & Med. **32**:1492, 1935. White, Garrey and Atkins.[10]

partial resection of the third and fourth left ribs. The pericardial sac was opened, and the ramus descendens of the left coronary artery was exposed. The vessel was isolated from the myocardial tissue sufficiently to pass a ligature around it. This ligature was led through the thoracic cavity to the surface by use of a small straight cannula. The cannula was sutured tightly into the wound so that pneumothorax was not a postoperative complication. After this procedure the dogs were allowed to regain consciousness, and when fully alert, three to four hours after operation, they were ready for observation of responses to sudden occlusion of the coronary vessel. Electrocardiograms were recorded after the operation and during the pain tests. It should be emphasized that in no case was the animal allowed to suffer unnecessarily.

PROTOCOL 1 (dog 195-43).—Three and one-half hours postoperatively, the dog was active and seemed fairly normal. Traction was applied to the ligature for fifteen seconds. This caused the dog to shift about, and toward the end the left leg was lifted. Respirations became definitely depressed. The mild restlessness disappeared as soon as the traction was released. After a rest period, an occlusion of eighteen seconds produced definite depression in the respiratory excursion. At the end of eighteen seconds, the ligature severed the artery. No changes were noted for ten to fifteen seconds. After this there were violent whining and stiffening of the legs, particularly the front legs. At autopsy, it was found that the ramus descendens had been divided 1.5 cm. from its origin.

PROTOCOL 2 (dog 230-43).—Four hours after operation, the dog was up and around the cage and was fairly active. Occlusion lasting fifteen seconds produced repeated lifting of the left foreleg and respiratory depression. After a rest period, occlusion of the artery for twenty seconds resulted in a repetition of the symptoms described and, in addition, the left foreleg was held in a cramped flexed position. A rest period was allowed, and the next occlusion lasted one minute. The animal repeatedly tried to move away. There was no movement of either leg. A rest period followed. The fourth occlusion lasted two minutes. About five seconds after the beginning, the left foreleg was lifted for a few seconds. The fifth occlusion also lasted two minutes. There was some lifting of the left foreleg and a tendency of the dog to pull away. At autopsy the ligature was found around the ramus descendens, 12 mm. from the aortic origin of the left coronary artery.

PROTOCOL 3 (dog 274-43).—In about three hours the animal had recovered consciousness and was alert and active. The duration of the first occlusion was one minute. A few seconds after application of traction, the animal became restless, kicking with his left hindleg and left forepaw. He whined and threw his head about. These signs disappeared immediately after release of the ligature. A short time after this, the artery was occluded for one minute, restlessness and a shifting of the left foreleg and hindleg being produced. The next occlusion lasted one minute. A few seconds after occlusion the dog became restless moving all four legs. There were some whining and tossing the head about. None of the signs persisted after the occlusion was released. At autopsy the ligature was found around the ramus descendens, 1.8 cm. from the origin of the left coronary artery.

PROTOCOL 4 (dog 287-43).—The dog recovered full consciousness in about two hours. Occlusion for one minute was followed by yelping, and the animal became restless and tried to change his position. All these signs disappeared immediately on release of the occlusion. After a rest period, an occlusion lasting

one minute was produced. Slow grunting respirations followed but stopped as the ligature was released. A third period of occlusion lasting one minute immediately produced restlessness, and respirations became moderately labored. After a recovery period, a fourth occlusion lasting one minute produced restlessness and the respirations became grunting in character. These signs lasted for only thirty seconds, after which the animal seemed comfortable in spite of the fact that traction was maintained for a full minute. The fifth occlusion, lasting one minute and thirty seconds, resulted in restlessness and a tendency to pull away. At autopsy, the ligature was found around the ramus descendens, 1.5 cm. from the aortic origin of the left coronary artery.

PROTOCOL 5 (dog 295-43).—About three hours after the operation had been completed, the animal was fully recovered from the anesthetic. Occlusion for one minute resulted in grunting respirations. The animal became restless and pulled away, with stiffening of the left foreleg. At the release of traction, all signs disappeared. After a recovery period, occlusion for one minute produced slight restlessness and respirations became more labored. The third occlusion lasted one minute. Again there was an immediate change, respirations becoming slower and grunting in character. This was associated with pronounced restlessness. These signs disappeared promptly with the release of the ligature. At autopsy the ligature was found around the ramus descendens, 1.5 cm. from the aortic origin of the left coronary artery.

PROTOCOL 6 (dog 297-43).—In about three hours the dog had completely recovered from the anesthetic. The artery was occluded for one minute. The animal became restless and had to be held down. Respirations became much slower throughout the period of occlusion, and the dog remained tense. The struggling at the beginning of the occlusion lasted only about ten seconds. As soon as the traction was released, all signs disappeared. After a recovery period, the second occlusion, lasting two minutes, produced no change except a slight slowing of respiration. The third occlusion was maintained for one minute. There was no change for five seconds; then there was mild struggling, lasting ten to fifteen seconds. During the last thirty seconds, the animal demonstrated no signs of pain. At autopsy the ligature was found around the ramus descendens, 1.7 cm. from the aortic origin of the left coronary artery.

PROTOCOL 7 (dog 300-43).—The dog recovered consciousness and was in poor general condition three hours after operation. Occlusion of the coronary artery for thirty seconds produced no change in the demeanor or activity of the dog. After a rest period, the artery was occluded for one minute. There was no change except a slowing of respirations. The next occlusion was maintained for two minutes. Again no changes were observed except minor ones in respiration. The lack of more dramatic responses in this dog may be due to his poor condition. There were subcutaneous emphysema and considerable pneumothorax. At autopsy the ligature was around the ramus descendens, 1.8 cm. from the aortic origin of the left coronary artery.

PROTOCOL 8 (dog 303-43).—Three hours after operation the dog was in fairly good condition and conscious. Occlusion of the coronary artery for thirty seconds immediately produced stretching of the left foreleg. The dog became restless and tried to move. Respirations tended to become slower and deeper. After a recovery period, a second occlusion lasting thirty seconds immediately resulted in respiratory changes. The animal became slightly restless and scratched with his back legs at the left foreleg. The third occlusion of thirty seconds' duration resulted in immediate respiratory changes and stretching of the right foreleg. There were slight changes

in the position of the head. The pupils were dilated. The fourth occlusion lasting thirty seconds brought forth only respiratory changes. At autopsy the ligature was around the ramus descendens, 1.8 cm. from the aortic origin of the left coronary artery.

PROTOCOL 9 (dog 305-43).—The dog made a good recovery from the operation and was fairly active in his cage three hours later. Five seconds after occlusion of the coronary artery by traction on the ligature, both strands of the ligature parted. In this short interval the animal exhibited a dramatic response. He whined loudly and became extremely restless, having to be held down. All this subsided as the ligature parted. At autopsy the ligature was around the ramus descendens, 1.2 cm. from the aortic origin of the left coronary artery.

PROTOCOL 10 (dog 306-43).—Three and one-half hours after operation the dog was conscious and in a fairly good condition. Traction on the ligature for thirty seconds immediately produced movements of the left foreleg and restlessness, which was pronounced for the first ten seconds and then subsided. There was some whining fifteen seconds after the beginning of the occlusion. Respiratory changes were recorded. All signs disappeared when traction was released. After

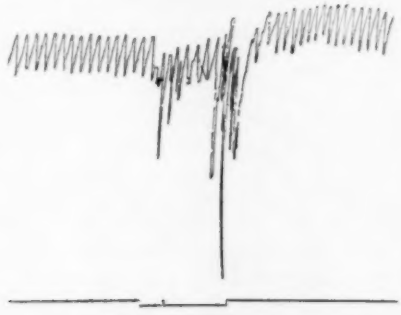


Fig. 2 (dog 306-43).—A typical tracing of the respiratory changes observed during traction on the coronary ligature in the control group of dogs. The period of traction is indicated by the break in the base line.

a rest period, the second occlusion of the artery was maintained for thirty seconds. During the first ten seconds the animal showed no changes. Then he started to move his left foreleg and became restless. Fifteen seconds after the beginning of the traction he got up and had to be restrained. These signs subsided shortly after release. The third occlusion was maintained for thirty seconds. Ten seconds later the animal was stretching the left foreleg and both back legs. The fourth occlusion lasted thirty seconds. Five seconds after the beginning of occlusion, the animal started to move his head. Twenty-five seconds later he became restless and attempted to get up. The animal immediately became quiet when traction was released. At autopsy the ligature was around the ramus descendens, 0.8 cm. from the aortic origin of the left coronary artery.

Summary.—Ten dogs were used in this series. Seven gave responses of a high degree, which were graded 3 plus; 2 gave fairly good positive responses (2 plus), and 1 did not respond (1 minus). In the last, the negative result was obviously partly if not totally due to the poor condition of the animal at the time of the test.

Group II (Dogs Prepared in Advance by Pericoronary Neurectomy).—The animals were anesthetized with intratracheal ether or pentobarbital sodium intravenously, and respirations were maintained mechanically. The heart was exposed through a partial resection of the third and fourth left ribs. The pericardial sac was opened. The left lung was reflected downward and maintained in position by a Mikulicz pad. A small piece of moist cotton was inserted under the left auricular appendage to maintain the latter away from the operative field. The pulmonary artery was freed from the aorta at the base of the heart and reflected to the right. The space between these two vessels was well exposed by careful dissection. All the nerve branches emerging from this area and coursing along either the coronary vessels or the myocardium itself were resected over a length of 10 to 15 mm. The epicardial tissue over the left coronary artery was incised and resected from the origin of the vessel down to a few millimeters below the bifurcation. Nerve branches

Fig. 3 (dog 302-43).—A typical tracing of the respirations observed during traction on the coronary ligature in the group of dogs prepared in advance by pericoronary neurectomy. The period of traction is indicated by the break in the base line.

emerging from the posterior aspect of the aorta and coursing along the left coronary artery were resected. Afterward, the left coronary artery, being well freed from its bed, was gently scraped and phenolized. The pericardium was closed. The chest was sutured after aspiration. Electrocardiograms were taken before and after operation.[12]

These dogs were kept for a period of approximately one month. Then, during a second operation, the ramus descendens was exposed and prepared for the cardiac pain test, as in the first group. The group of dogs with pericoronary neurectomy were prepared by M. Fanteux, and the pain experiments of both groups were carried out by O. Swensen.

Protocol 1 (dog 299-43).—One month after pericoronary neurectomy, the animal, which had been in excellent condition since the operation, was prepared for the pain test. Three hours after the second operation the animal was alert and moving around the cage. The periods of occlusion of the coronary artery, lasting one minute, thirty seconds and forty seconds, with rest periods between, were performed, with no changes in the animal. At autopsy the ligature was around the ramus descendens, at 2.8 cm. from the aortic origin of the left coronary artery.

Protocol 2 (dog 302-43).—Thirty-five days after pericoronary neurectomy, the animal, which had been in excellent condition since the operation, was prepared for the pain test. Three hours after the second operation the dog was fairly active, moving around in his cage. Four periods of occlusion, each of thirty seconds'

12. These will be reported in a separate communication.

duration, resulted in no changes in the animal. At the end of the last period of occlusion, the vessel divided and there was a large amount of bleeding through the cannula. This did not seem to disturb the animal. He was killed. At autopsy the ligature was around a large vessel, which proved to be the first branch of the ramus descendens. This branch was emerging from the ramus descendens, 2 cm. from the aortic origin of the left coronary artery.

Protocol 3 (dog 313-43).—Thirty-one days after pericoronary neurectomy, the animal, which had been well since operation, was prepared for the pain test. Three hours later, he was active in his cage. Traction was applied during thirty seconds. There was no change in the position or demeanor of the dog. A rest period followed. There was a second period of traction during thirty seconds. The dog showed no change whatsoever except at the end, when he moved, changing his position slightly. A rest period was followed by a third period of traction for thirty seconds. Again there was no sign of discomfort. The characteristic movement of the left foreleg was absent. The behavior of this dog during the three tests was striking in comparison to the dogs in the control series. An interesting fact is that during the first traction, an attack of ventricular paroxysmal tachycardia developed, which did not produce primary ventricular fibrillation. Often these attacks after sudden coronary occlusion are followed in dogs with intact heart by primary ventricular fibrillation (fig. 4). At autopsy the ligature was around the ramus descendens, 1.5 cm. from the aortic origin of the left coronary artery.

Fig. 4. (dog 313-43).—Lead II, taken during the first occlusion. Paroxysmal ventricular tachycardia is demonstrated. This was not followed by primary ventricular fibrillation, as is often the case when this rhythm develops after sudden coronary occlusion.

Protocol 4 (dog 317-43).—Thirty-three days after pericoronary neurectomy, the animal, which had been in excellent condition since the operation, was prepared for the pain test. Three hours after the second operation he was conscious, being up and around his cage. Three periods of occlusion, each of thirty seconds' duration, with adequate rest periods, produced no change in the animal. The fourth occlusion lasted thirty seconds. The result this time was somewhat questionable in that at the end of the period the dog was restless. Two more periods of occlusion, each lasting thirty seconds, were carried out. The animal showed no change. At autopsy the ligature was around the ramus descendens, 1.3 cm. from the aortic origin of the left coronary artery.

Protocol 5 (dog 339-43).—Thirty-one days after pericoronary neurectomy, the healthy animal was prepared for the pain test. Occlusion for thirty seconds was followed by movement of the left foreleg. A second occlusion, of forty-five seconds' duration, resulted in no change. After a rest period, the third occlusion lasted forty-five seconds. There was no change until the middle of the test, when there was a slight movement of the left foreleg. The last occlusion, of one minute's duration, resulted in no change. At autopsy the ligature was around the ramus descendens, 2 cm. from the aortic origin of the left coronary artery.

PROTOCOL 6 (dog 340-43).—Thirty-two days after pericoronary neurectomy, the well animal was prepared for the pain test. Three hours after the second operation the dog was lively and fairly normal appearing. The first occlusion lasted thirty seconds. About two seconds after occlusion there was a slight movement of the left forefoot. This was not repeated, and there were no other changes in the position of the dog. After a recovery period, a second occlusion was maintained for one minute. Five seconds after onset the animal moved. He again moved, about fifty seconds later. No other signs were noted. It must be said that this animal was extremely active and it was hard to make him stay still during the rest periods. It was, therefore, difficult to interpret the movements he made during occlusion of the coronary artery. At autopsy the ligature was around the ramus descendens, 2.2 cm. from the aortic origin of the left coronary artery.

PROTOCOL 7 (dog 5-44).—Thirty-six days after pericoronary neurectomy the animal was submitted to the pain test. When the experiment began, the dog was completely awake and not nervous. Three periods of occlusion, of thirty, sixty and sixty seconds' duration, with adequate rest periods, produced no change in the animal. At autopsy the ligature was around the ramus descendens, 2.1 cm. from the aortic origin of the left coronary artery.

PROTOCOL 8 (dog 8-44).—Thirty-eight days after pericoronary neurectomy, the well animal was submitted to the pain test Three hours after operation the animal was awake and lively. The first occlusion lasted thirty seconds. The dog swayed; yet there were no movements of the legs and no struggle. There was a rest period, during which the dog was continuously moving and playful. The second occlusion, of one minute's duration, resulted in two movements of the left foreleg. The next occlusion was maintained for one minute. There was no change of behavior during this final test. At autopsy the ligature was around the ramus descendens, 1.8 cm. from the aortic origin of the left coronary artery.

PROTOCOL 9 (dog 9-44).—Thirty-nine days after pericoronary neurectomy, the animal was submitted to the pain test. At the time of the experiment, he was completely awake and active. Occlusion for thirty seconds resulted in some movement during the first ten seconds. After a rest period, the second occlusion lasted for thirty seconds. There were definite movement of the left foreleg and slowing of the respirations. The third occlusion lasted one minute and produced no change. The fourth occlusion, of one minute's duration, produced some movement of the left foreleg. At autopsy the ligature was around the ramus descendens, 1.2 cm. from the aortic origin of the left coronary artery.

PROTOCOL 10 (dog 58-44).—Forty-eight days after pericoronary neurectomy, the well animal was submitted to the pain test. At the time of the experiment, he was completely awake and active. Four periods of occlusion, the first of thirty seconds' duration and the rest of one minute's duration, produced no changes. At autopsy the ligature was around the ramus descendens, 2.1 cm. from the aortic origin of the left coronary artery.

Summary.—Ten dogs were used in this series. Six gave no responses at all (3 minus); 1 was irresponsive in five occlusions, and in 1 the result was questionable, because the animal seemed restless (2 minus); 2 gave doubtful reactions; they were active during the rest periods, and it is difficult to conclude whether the activity they presented during the tests was due to pain or whether it was just normal behavior. Only 1 had a positive reaction, which was graded 1 plus.

COMMENT

It is generally agreed that the nerve fibers carrying pain impulses from the heart and coronary blood vessels follow the course of the coronary vessels. Woolard [13] has shown that the nerves to and from the ventricles are concentrated for the most part around the coronary vessels, forming a loose spiral network, and that they congregate for the most part around the origins of the coronary arteries before passing over to plexuses located between the pulmonary artery and the aorta and on the anterior surface of the aorta. Katz and Saphir [14] stimulated the nerve plexus between the aorta and the pulmonary artery. They found that both pressor and depressor fibers are present in this plexus and that the concentration of the afferent fibers forms a sort of "internal capsule," which they say may be important for other types of afferent fibers, such as those carrying pain. When the plexus was cauterized, the reflexes were abolished in the three experiments in which it was done. Sutton and Lueth [8] painted the wall of the ramus descendens of the left coronary artery with alcohol in four experiments and then repeatedly occluded the artery by pulling on the ligature, without producing pain. They considered that the pain fibers involved in experimental occlusion of the coronary artery are the nerve fibers that are found in the adventitia of the coronary artery or in the immediate surrounding tissues and that the cutting of this pathway prevents the transmission of pain. Mayne and Katz [15] were among the first to recognize the importance of interrupting the pain fibers as near the heart as possible not only for the essential reason of not missing any but for the purpose of avoiding the severance of important nerve branches to the lungs, which is not without certain serious risks.[10] They sectioned the nerve plexus in the posterior mediastinum of the dog in three experiments. It was found that traction on the ligature around the coronary vessel gave no more effective response, although stimulation of the somatic sensory nerve gave the usual response.

Our experimental results are in accordance with those of the aforementioned workers. Pericoronary neurectomy when technically well done

13. Woolard, H. H. J.: The Innervation of the Blood Vessels, Heart **13**:319, 1927.

14. Katz, L. N., and Saphir, O.: The Nerve Plexus Between the Aorta and Pulmonary Artery, Am. J. Physiol. **104**:253, 1933.

15. Mayne, W., and Katz, L. N.: Observations on the Path Taken by the Pain Fibers from the Heart, Am. J. Physiol. **114**:688, 1936; Katz, L. N.; Mayne, W., and Weinstein, W.: Presence of Pain Fibers in the Nerve Plexus Surrounding the Coronary Vessels, Arch. Int. Med. **55**:760 (May) 1935.

16. Cromer, S. P., and Ivy, A. C.: Respiratory Death from Central Vagus Stimulation After Removal of Stellate Ganglia, Am. J. Physiol. **104**:457, 1933. Cromer, S. P.; Young, R. H., and Ivy, A. C.: On the Existence of Afferent Respiratory Impulses Mediated by the Stellate Ganglia, ibid. **104**:468, 1933.

abolishes pain. Furthermore, it has the advantage of avoiding section of nerve pathways to other vital structures. Careful observation of more than 50 dogs operated on has demonstrated to one of us (M. F.) that the operation is harmless to cardiac functions. The heart apparently can still adapt itself to the strains of increased activity. Finally, the results obtained in 2 patients [17] who were treated by pericoronary neurectomy combined with ligation of the great cardiac vein seem to be identical to the experimental results reported in this paper and seem to substantiate the view acquired in experimental work that pericoronary neurectomy is not deleterious to the cardiac functions. One was operated on Sept. 11, 1944. The other was operated on June 6, 1945. Both were experiencing pain at the slightest exertion and were unable to work. The first patient has never presented anginal pains since the operation, and he is now working every day, showing that this operation not only blocked the fibers carrying pain sensation but seemed to improve the cardiac function. The second patient has not been permitted to resume his work as yet. However, it is gratifying to note that he can go up and down the stairway four and five times a day and walk on the street for a long distance without experiencing any discomfort. We are well aware that it is too early to reach any final judgment regarding this new procedure; yet the experimental and clinical results seem to justify further clinical trial.

SUMMARY

1. Experiments carried on to test the effectiveness of pericoronary neurectomy in abolishing anginal pains in coronary disease are reported and discussed.

2. The experimental results obtained show that this procedure abolishes the signs which are considered reactions to pain in dogs submitted to the test originally described by Sutton and Lueth.

3. Clinical results in 2 patients treated by pericoronary neurectomy combined with ligation of the great cardiac vein seem to confirm the experimental findings.

17. Since the time of submission of this communication, 7 additional patients have been treated by this operation.

INTRAPERITONEAL ADMINISTRATION OF SUCCINYLSULFATHIAZOLE AND PHTHALYLSULFATHIAZOLE

Their Use in the Prophylaxis and Treatment of Peritonitis

JOHN P. YOUNG Jr., M.D.
AND
WARREN H. COLE, M.D.
CHICAGO

SHORTLY after the introduction of the sulfonamide drugs as antibiotics, they were used intraperitoneally as a prophylaxis against peritonitis. Innumerable reports indicated that they were effective, but most surgeons abandoned their intraperitoneal use when penicillin was made available, because it appeared to be more effective than the sulfonamide compounds. Of these two drugs penicillin appears definitely to be more helpful against colon bacilli, but neither can be classified as being extremely effective against these organisms. Although streptococci and other pyogenic bacteria are occasionally isolated as causative organisms in peritonitis Escherichia coli is much commoner and even when a mixed infection occurs it is usually the predominant organism. Therefore, in the treatment or prophylaxis of peritonitis there would appear to be a need for an antibiotic agent which would be more effective against Esch. coli.

The introduction of the oral use of succinylsulfathiazole in 1941 by Poth and Knotts [1] and, later, phthalylsulfathiazole in 1943 by Poth and Ross [2] led us to investigate the absorbability of these drugs when they were introduced intraperitoneally. Experiments performed by us, as described later, revealed the fact that they were absorbed rapidly from the peritoneal cavity, although they are absorbed only to the slightest extent when given by mouth.

Poth,[3] Poth and Knotts,[4] Streicher [5] and Poth and Ross [6] have shown that when given orally succinylsulfathiazole and phthalylsulfathiazole are capable of reducing the number of bacteria (particularly Esch. coli)

Mr. Everett Hoppe gave able assistance.

Aided by a grant from Sharp & Dohme, Inc.

From the Department of Surgery, University of Illinois College of Medicine and the Illinois Research and Educational Hospitals.

1. Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, Arch. Surg. **44**:208 (Feb.) 1942.

2. Poth, E. J., and Ross, C. A.: Phthalylsulfathiazole, a New Bacteriostatic Agent, Federation Proc. **2**:89, 1943.

(Footnotes continued on next page)

in the feces to a remarkably low number. This has led to a rather widespread oral use of these drugs in colonic surgery. Large doses of the drugs have been administered, without detectable damage to the laboratory animals or to the patients. This has been thought to be merely a reflection of one of the physical properties of the drugs, namely, the low rate of absorption from the gastrointestinal tract. Per gram of drug, phthalylsulfathiazole is about twice as effective as succinylsulfathiazole. Toxic manifestations have been minimal or entirely absent in patients receiving 0.15 to 0.25 Gm. of succinylsulfathiazole or 0.08 to 0.12 Gm. of phthalylsulfathiazole per kilogram of body weight by mouth per day.

EXPERIMENTS ON ANIMALS

Succinylsulfathiazole.—We made a sterile suspension of succinylsulfathiazole in isotonic solution of sodium chloride and, under sterile precautions, injected (with a syringe and needle) 0.25 Gm. of the drug per kilogram of body weight into the peritoneal cavities of 8 dogs. Samples of blood were taken every four hours for thirty-two hours. As shown in the chart (*A*), the maximum level (2.5 mg. per hundred cubic centimeters) was noted at four hours.

None of the dogs evinced signs of toxicity. One dog was explored at the end of twenty-four hours to allow inspection of the peritoneal cavity. There were small clumps of the drug on the folds of mesentery, and this was estimated to represent about 20 per cent of the quantity of the drug placed therein. There was only a moderate amount of peritoneal fluid, and there was no evidence of peritoneal irritation. The incision was closed, and the animal recovered without further difficulty.

The abdomen of a second dog was opened at the end of forty-eight hours and the peritoneal cavity inspected. The succinylsulfathiazole had been completely absorbed, and again there were no signs of irritation. There were a few fibrinous adhesions between the omentum and the site of the needle puncture.

The remaining 6 dogs were operated on at intervals up to twenty-one days and similar observations made. No trace of the drug could be found; likewise, peritoneal irritation was absent or minimal.

---

3. Poth, E. J.: The Sulfonamides as Therapeutic Agents in Intestinal Antisepsis: Collective Review, Internat. Abstr. Surg. **78**:373, 1944; in Surg., Gynec. & Obst., May 1944; Succinylsulfathiazole: An Adjuvant in Surgery of the Large Bowel, J. A. M. A. **120**:265 (Sept. 26) 1942.

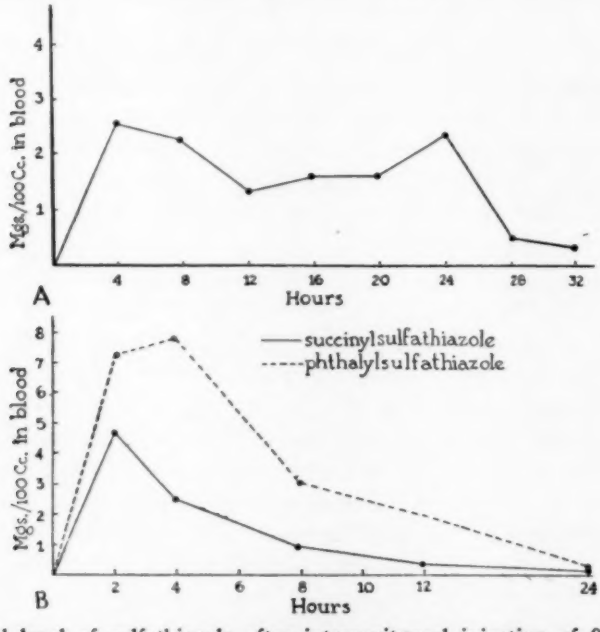
4. Poth, E. J.; Knotts, F. L.; Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: I. Succinylsulfathiazole, a New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, Arch. Surg. **44**:187 (Feb.) 1942.

5. Streicher, M. H.: Phthalylsulfathiazole, J. A. M. A. **129**:1080 (Dec. 15) 1945.

6. Poth, E. J., and Ross, C. A.: The Clinical Use of Phthalylsulfathiazole, J. Lab. & Clin. Med. **29**:785 (Aug.) 1944.

Dog 1 was reoperated on at thirty days, and no evidence of damage to the peritoneal cavity was found. Dog 2 was likewise reoperated on at fourteen days, and similar results were noted.

In order to study the toxic effects of massive doses of succinylsulfathiazole, we injected 5 Gm. of the drug per kilogram of body weight into the peritoneal cavities of 2 dogs. Both were dead in thirty-six hours. Histologic studies revealed diffuse pneumonitis throughout both lungs. There was about 300 cc. of yellow fluid in the peritoneal cavity. No drug crystals were demonstrable in the kidney.



A, blood level of sulfathiazole after intraperitoneal injection of 0.25 Gm. per kilogram of body weight of succinylsulfathiazole in the dog. The graph represents the average of 8 dogs. Note that the blood level is lower but maintained longer than with the smaller dose used in human beings (see *B*). *B*, blood level of sulfathiazole after implantation of 0.1 Gm. per kilogram of body weight of succinylsulfathiazole, as compared with the level following implantation of phthalylsulfathiazole into the peritoneal cavity of human beings at the time of operation. Each graph represents the average in 12 patients.

Into a series of 8 dogs 2.5 Gm. of the drug per kilogram of body weight was injected intraperitoneally. Three of the 8 dogs vomited within one hour after injection, but at no time did they appear acutely ill. One dog died nine days later, and at autopsy it was apparent that the liver and small bowel had been punctured at the time of injection. The dog had struggled violently while the needle was in place, and from the second day on he appeared listless and failed to eat as well as the other dogs under study. There was a walled-off cavity containing about 30 cc. of bile-stained fluid, and there was a localized

abscess about a loop of ileum. Dissection revealed a small hole in the wall of the bowel. The peritoneum was covered with a fibrinous exudate.

The remaining 7 dogs were killed at intervals up to thirty days. There was no evidence of peritoneal irritation in any of the dogs, and the histologic studies did not reveal parenchymal damage to any of the visceral organs.

Phthalylsulfathiazole.—Into the peritoneal cavities of 4 dogs 5 Gm. of phthalylsulfathiazole per kilogram of body weight was injected as a suspension in isotonic solution of sodium chloride. All 4 dogs vomited within thirty minutes; 2 dogs died within twenty-four hours. Autopsies revealed approximately 300 cc. of yellow peritoneal fluid and diffuse hyperemia of all parenchymatous organs. About 25 per cent of the drug injected was found well distributed throughout the peritoneal cavity.

Six dogs were given 2.5 Gm. of phthalylsulfathiazole intraperitoneally per kilogram of body weight. All 6 dogs vomited within thirty minutes. Two dogs died within twenty-four hours, but the other 4 dogs remained alive and after their initial vomiting seemed to suffer no evil effects.

Four dogs were given 1 Gm. of the drug per kilogram of body weight intraperitoneally. All the dogs vomited but remained alive and well. Two dogs were killed, 1 at seven and another at fourteen days, and histologic sections of the visceral organs were studied. Aside from a mild hyperemia at seven days, no pathologic changes were noted.

INTRAPERITONEAL USE OF THE DRUGS IN HUMAN BEINGS

In a clinical study of the intraperitoneal use of succinylsulfathiazole and phthalylsulfathiazole,[7] a dose was adopted which would be no greater than 0.1 Gm. per kilogram of body weight. Since animals tolerated a dose of at least 1 Gm. per kilogram of body weight, given intraperitoneally, without any evidence of toxic reaction with either drug, the dose of 0.1 Gm. per kilogram of body weight for human beings would appear to be entirely safe.

Up to date we have used succinylsulfathiazole in 28 patients and phthalylsulfathiazole in 23 patients intraperitoneally [8] in a dose of 6 Gm. for an adult, which is approximately 0.1 Gm. per kilogram of body weight. The drug has been dusted in as a powder or suspended in 20 to 30 cc. of isotonic solution of sodium chloride and poured into the peritoneal cavity. Care must be taken lest the drug get into the wound,

7. We are informed by Dr. M. Streicher of Chicago that he has also used both of these drugs intraperitoneally as a prophylaxis against postoperative peritonitis.

8. The drugs were sterilized by heating in a dry oven for four hours at a temperature of 140 C.

since experiments on animals conducted by one of us (J. Y.) have shown that its presence in a wound will delay healing. This is to be expected since neither of the two drugs, unlike other sulfonamide compounds, is absorbed from subcutaneous tissue.

The patients were watched carefully postoperatively for signs of toxic manifestations, such as hematuria, oliguria, leukopenia, agranulocytosis, nausea, vomiting, headache and mental confusion; specimens of blood were drawn at specified intervals up to twenty-four hours for determinations of blood levels. In none of the patients did we observe any evidence of toxic reaction to either of the two drugs; results of urinary examinations also were consistently normal.

Two cases were of particular interest to us since they gave us an opportunity to study the effect of phthalylsulfathiazole on established peritonitis. One of the patients was a Negro boy, 10 years old, who entered the Research and Educational Hospitals with a history of abdominal pain of five days' duration. Examination revealed general peritonitis arising from a perforated appendix. He had been treated at home with catharsis and enemas, and at the time he entered the hospital he was irrational, dehydrated, toxic and almost preterminal. Since children with perforated appendixes respond so poorly to conservative or delayed surgical treatment, it was thought that operation should be performed as soon as dehydration and electrolyte imbalance could be corrected. After several hours of preoperative treatment, operation was performed; the appendix was removed and an abscess drained although it was obvious that general peritonitis also existed. Culture revealed Esch. coli, hemolytic Staphylococcus aureus and a nonhemolytic streptococcus. Four grams of phthalylsulfathiazole was placed in the peritoneal cavity. The administration of penicillin, which had been started preoperatively in doses of 30,000 units every three hours, was continued. The patient died four days later, and at autopsy the peritoneal exudate was again cultured. The cultures revealed numbers of hemolytic Staph. aureus and nonhemolytic streptococci, but no Esch. coli were found. Another patient illustrated the same point, namely, disappearance of Esch. coli in the peritoneal cavity following implantation of phthalylsulfathiazole into the peritoneal cavity, although streptococci and staphylococci were still present on culture. In a Negro woman, aged 23 years, a spontaneous perforation of the cecum developed at the site of a tuberculous ulcer. At operation, which was delayed twelve hours because of the patient's refusal to give permission for operation, there was generalized peritonitis along with disseminated tuberculous peritonitis. The perforated cecum was exteriorized, and 6 Gm. of phthalylsulfathiazole was implanted in the peritoneal cavity before closure. Culture of material taken at the time of operation revealed Esch. coli, streptococci and staphylococci. Roentgenologic examination of the chest revealed

minimal tuberculosis of the lungs. At autopsy, three days later, which confirmed the operative findings, culture revealed no Esch. coli but numerous colonies of streptococci and staphylococci. The patient had been given heavy doses of penicillin (300,000 units per day) beginning with the date of operation.

We admit that no conclusions can be drawn from these cases, but since penicillin is known to be much less effective against colon bacilli than against pyogenic organisms one would be inclined to attribute the elimination of the infection with colon bacilli to the phthalylsulfathiazole rather than to penicillin, particularly since we know that it is so effective against that organism in the intestinal tract. However, it is important to note that intensive pencillin therapy failed to eliminate the streptococci and staphylococci in both instances.

ANALYSIS OF RESULTS

In clinical trials on human beings as well as in experiments on dogs, we noted that succinylsulfathiazole and phthalylsulfathiazole were absorbed rapidly from the peritoneal cavity. The peak blood level occurs within the first few hours after implantation.

In none of the patients receiving the drugs in the dose of approximately 0.1 Gm. per kilogram of body weight was there any evidence of toxic reaction. Routine urinary examinations revealed no albumin, red blood cells, crystalluria or any other pathologic change. This freedom from abnormal urinary findings is perhaps explained on the basis that the kidneys do not excrete large amounts of either drug (Poth and Ross [6]) in the free form and that the conjugated form is soluble at a p_H as low as 5.61. Nevertheless, we were careful to insure a daily fluid intake of at least 2,500 cc.

In dogs it had been determined that 2.5 Gm. of succinylsulfathiazole per kilogram of body weight could be used without serious side effects and that 1 Gm. per kilogram of phthalylsulfathiazole could likewise be used intraperitoneally with safety. Hence we felt entirely safe in using 0.1 Gm. per kilogram of body weight in human beings; subsequent observations seemed to justify that dose.

From the previous study by Walter and Cole [9] and others, we know that clumping of the sulfonamide drugs in the peritoneal cavity will lead to a foreign body reaction; accordingly we are careful to distribute the drug diffusely. When the drug is suspended in isotonic solution of sodium chloride, there is less danger of clumping. Neither of the two drugs studied showed any tendency to produce intra-abdominal adhesions, thereby resembling sulfanilamide; it is well known that sulfathiazole and

9. Walter, I., and Cole, W. H.: The Intraperitoneal Administration of Sulfadiazine, Surg., Gynec. & Obst. **76**:524 (May) 1943.

sulfadiazine produce a few adhesions following implantation in the abdominal cavity, but they disappear after six to ten days.

Determinations of the blood levels of sulfathiazole in patients having 0.1 Gm. succinylsulfathiazole or phthalylsulfathiazole placed in their peritoneal cavities reveal that a peak is reached rapidly (see chart, *B*), but that the peak is maintained for only a short time. This would not appear to be entirely desirable. However, since the purpose of implantation of a sulfonamide drug into the peritoneal cavity is to combat soilage incurred at the time of operation and could not be expected to offer much protection against a leaking suture line, which usually occurs only after a few days, perhaps the need for prolonged exposure is not so urgent. From the standpoint of slow absorption sulfadiazine and sulfathiazole are superior to the two drugs being discussed, but since these two drugs are so ineffective against Esch. coli they have been supplanted by penicillin. Some authors have reported penicillin to be mildly effective against Esch. coli, but our experience with penicillin in Esch. coli infections has been disappointing. Preliminary reports concerning streptomycin are encouraging in infections with colon bacilli; it is therefore possible that this drug given along with penicillin would eliminate indications for intraperitoneal implantation of any drugs.

That phthalylsulfathiazole is effective against colon bacilli in the peritoneal cavity is suggested by histories of 2 cases discussed previously in this report. Penicillin had failed to eliminate the staphylococci and streptococci from the peritoneal exudate in both cases, but the colon bacilli had been eliminated; we are inclined to attribute this effect on the colon bacilli to phthalylsulfathiazole and not to penicillin.

Because of the preliminary nature of this report, we have not attempted to evaluate the efficacy of succinylsulfathiazole or phthalylsulfathiazole in reducing postoperative peritonitis or other complications. In view of the low incidence of postoperative peritonitis in carefully performed intestinal anastomoses, it will be necessary to study several hundred cases before definite conclusions can be reached on this point.

SUMMARY

When succinylsulfathiazole and phthalylsulfathiazole are implanted in the peritoneal cavities of human beings or dogs, they are rapidly absorbed into the blood stream; the average peak level of the two drugs at four hours was 4 versus 5 mg. per hundred cubic centimeters respectively (see chart, *B*). The rate of disappearance from the peritoneal cavity is much more rapid than that of sulfathiazole or sulfadiazine and resembles more closely the rate of disappearance of sulfanilamide. Adhesions of the type which are encountered experimentally for several days after intraperitoneal implantation of sulfadiazine and sulfathiazole (but which later disappear) are not observed after use of either drug.

Either of the drugs herein discussed can be given intraperitoneally to dogs in a dose of at least 1.0 Gm. per kilogram of body weight, without reaction. We have adopted a dose of 0.1 Gm. per kilogram of body weight for human beings, but, in view of the low toxicity in animals, it would appear that the dose could be increased in human beings over that which we used; we noted no toxic reactions of any type in any of the patients to whom the drug had been given.

Our series of cases is too small to allow us to compare it with a control series, since the incidence of significant postoperative intraperitoneal infection which this therapy would hope to prevent is too small to allow comparison unless several hundred cases were studied. However, since both drugs are known to be extremely effective in reducing the Esch. coli count of the stool when they are given orally, it might be reasonable to suppose that they would also be effective against that same organism occuring as a contaminant following intestinal resection.

We are unable to predict which of the two drugs would be the more effective, but since the blood level following a given dose of each is slightly higher and more prolonged with phthalylsulfathiazole this drug might be expected to be more effective than succinylsulfathiazole.

LYMPHADENOID GOITER

Its Differentiation from Chronic Thyroiditis

CHARLES C. PARMLEY, M.D.
AND
C. ALEXANDER HELLWIG, M.D.
WICHITA, KAN.

WHILE in recent articles (Joll,[1] Graham,[2] Hellwig,[3] McSwain and Moore[4] and Schilling[5]) lymphadenoid goiter is recognized as a pathologic and clinical entity, the causes, histogenesis and clinical significance of this rare form of goiter are still little understood.

Since 1940, we have had the opportunity of observing 14 cases of lymphadenoid goiter. We are presenting the histologic data because we found alterations of the thyroid epithelium which have not been correctly interpreted in recent studies, and we believe that these epithelial changes, rather than the more conspicuous accumulations of lymphoid tissue, are the most important characteristics of this disease.

CLINICAL FINDINGS

The 14 patients were all women. While 2 patients were 16 and 27 years old respectively, the ages of all others ranged from 32 to 61 years, the average age being 44.7 years. The patients had noticed, from six weeks to twenty years previous to admission to the hospital, the following symptoms: 13 complained of enlargement of the thyroid, with or without pressure symptoms; 11 had noticed nervousness; 2 had rapid heart rates, 1 had sweating and tremor of the hands, and 1 had lost some weight.

Regarding sex life, the following data are of interest. Twelve of our patients were married, and 7 had from one to four children. Only 3 of the 14 patients had regular menses, 6 were in the menopause, 2 complained of dysmenorrhea and 1 had irregular periods. Physical examina-

From the Department of Pathology, St. Francis Hospital.

1. Joll, C. A.: The Pathology, Diagnosis and Treatment of Hashimoto's Disease (Struma Lymphomatosa), Brit. J. Surg. **27**:351, 1939.

2. Graham, A., and McCullaugh, E. P.: Atrophy and Fibrosis Associated with Lymphoid Tissue in the Thyroid, Arch. Surg. **22**:548 (April) 1931.

3. Hellwig, C. A.: Lymphadenoid Goiter, Arch. Path. **25**:838 (June) 1938.

4. McSwain, B., and Moore, S. W.: Struma Lymphomatosa, Surg., Gynec. & Obst. **76**:562, 1943.

5. Schilling, J. A.: Struma Lymphomatosa, Struma Fibrosa and Thyroiditis, Surg., Gynec. & Obst. **81**:533, 1945.

Clinical and Pathologic Findings

Case	Age, Yr.	Duration	Menses	Gynecologic Surgery	Clinical Diagnosis	Weight of Thyroid, Gm.	Gross Appearance	Stroma	Lympho-cytes, per Cent	Colloid	Acini	Hürthle Cells
1	44	2.5 yr.	Normal	None	Fetal adenoma	42	Diffuse	Scanty	40	Scanty	Small	Many
2	27	6 yr.	Dysmenorrhea	None	Nontoxic goiter	50	Diffuse	Scanty	20	Scanty	Small	Many
3	50	2 yr.	Surgical menopause	Hysterectomy	Colloid goiter	66	2 nodes	Scanty	25	Some	Small	Many
4	46	1 yr.	Beginning menopause	None	Nodular colloid goiter	70	2 nodes	Scanty	10	Scanty	Small	Many
5	36	3 yr.	Dysmenorrhea	None	Nodular colloid goiter	44	Diffuse	Scanty	50	Some	Small	Many
6	58	15 yr.	Menopause	None	Colloid goiter	50	Diffuse	Scanty	40	Some	Small	Many
7	32	7 mo.	Irregular	None	Diffuse colloid goiter	41	Diffuse	Scanty	40	Scanty	Small	Some
8	36	6 wk.	.....	None	Nodular colloid goiter	60	2 nodes	Scanty	20	Some	Small	Many
9	47	7 yr.	Menopause	Pelvic tumor	Fetal adenoma	27	Diffuse	Moderate	60	Scanty	Small	Few
10	61	15 yr.	Menopause	Hysterectomy	Nodular toxic goiter	30	1 node	Moderate	60	None	Small	Great many
11	16	1 yr.	.....	Brain tumor	Toxic goiter	28	2 nodes	Scanty	50	Some	Small	Many
12	38	2 yr.	Normal	Salpingectomy	Toxic goiter	24	Diffuse	Much	50	Some	Small	Few
13	36	20 yr.	Normal	Cæsarian section	Toxic goiter	42	Diffuse	Scanty	50	Scanty	Small	Some
14	48	?	Menopause	None	Toxic goiter	30	Diffuse	Scanty	20	None	Small	Some

tion revealed a variation in pulse rates from 64 to 88, while the blood pressures ranged from 100 to 150 systolic and 65 to 90 diastolic.

The preoperative diagnoses were nontoxic goiter in 8, fetal adenoma in 2 and toxic goiter in 4 cases. Three patients received preoperative treatment with strong solution of iodine, U. S. P., and the youngest patient had received iodine for six months previous to admission. In all the patients except 1 both lobes of the goiter were removed at operation. In only 3 patients were postoperative elevations of temperature above 101 F. observed. As a rule the patients were discharged from the hospital ten days after thyroidectomy.

Follow-up data were available from all except 2. No recurrence of the goiter was noticed. In 4 patients mild signs of decreased thyroid function appeared about six months after thyroidectomy. These symptoms were controlled satisfactorily by the administration of thyroid.

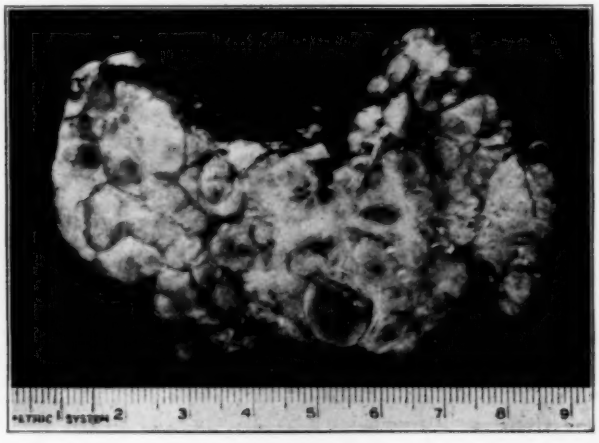


Fig. 1.—Lymphadenoid goiter (case 6). Diffuse grayish brown firm cut surface.

PATHOLOGIC FINDINGS

The surgical specimens weighed from 24 to 70 Gm., the average weight being 45.7 Gm. Since normal thyroids obtained in Wichita at autopsies of women in the fifth decade of life weigh 20.8 Gm. (Hellwig [6]), the lymphadenoid goiters represented a definite increase in weight over the normal.

The contours of the removed goiters were regular, and in only 1 case had the surgeon noticed firm adhesions to the surrounding structures. The cut surface was divided into distinct lobules, and the tissue in most specimens was uniform throughout. The tissue was light

6. Hellwig, C. A.: The Thyroid Gland in Kansas, Am. J. Clin. Path. **5**:103, 1935.

grayish brown, resembling pancreas, and had a firm consistency. In 5 cases small nodules were visible, which measured not more than 10 mm. in diameter, an incidence which conforms with our autopsy findings in normal thyroids of patients in this age group.

The microscopic pictures in our 14 cases were strikingly uniform. While the abundance of lymphoid tissue has been stressed by most observers as the most conspicuous feature, we found, by actual measurement of the lymphoid and epithelial tissue in paraffin sections, that only one third of the enlargement of the thyroid gland can be explained by proliferation of lymphoid tissue, while two thirds of the gland consisted of epithelial tissue. In our opinion, the accumulation of lymphoid tissue is a secondary phenomenon and represents a response of lymphocytes to an abnormal function and proliferation of thyroid epithelium.

Our findings on the thyroid epithelium were at variance with those of former observers and warrant more detailed consideration. Most of the acini were of small size and had oval or slitlike lumens. The epithelium was high cuboid and measured between 8 and 12 microns in height. The cytoplasm of these cells stained light bluish, and most of the cells were without evidence of degeneration. As a rule the lumens of these acini were without stained colloid but often contained groups of cells with dark nuclei and indistinct outlines. The latter have been regarded by most writers as desquamated acinar cells; however, one occasionally sees a bud of large histiocytes protruding through a defect in the acinar wall, and therefore it seems more probable that the origin of these intrafollicular cells is from wandering cells of tissue.

Foreign body giant cells attached to fragments of colloid or tubercle-like structures, which are common in chronic thyroiditis, were completely absent in our material.

More striking was another type of thyroid epithelium, which was present in every case of our series, namely pale large polygonal cells which resembled hepatic or adrenal cells much more than thyroid epithelium. These unusual cells were arranged either in acini with small lumens or in solid cell strands surrounded with lymphoid tissue. The size of these pale cells varied between 20 to 30 microns, their vacuolated cytoplasm took an intense stain with eosin and the nuclei were of varying size; often eccentric, they had a fine chromatin network and occasionally one or two small nucleoli.

While these large pale cells have attracted the attention of previous observers, there is disagreement in regard to their significance. Breunger [7] and Joll [1] regarded them as regenerative or hypertrophic, while the

7. Bruenger, H.: Ueber Operationstod bei Thyroiditis chronica, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **28**:213, 1915.

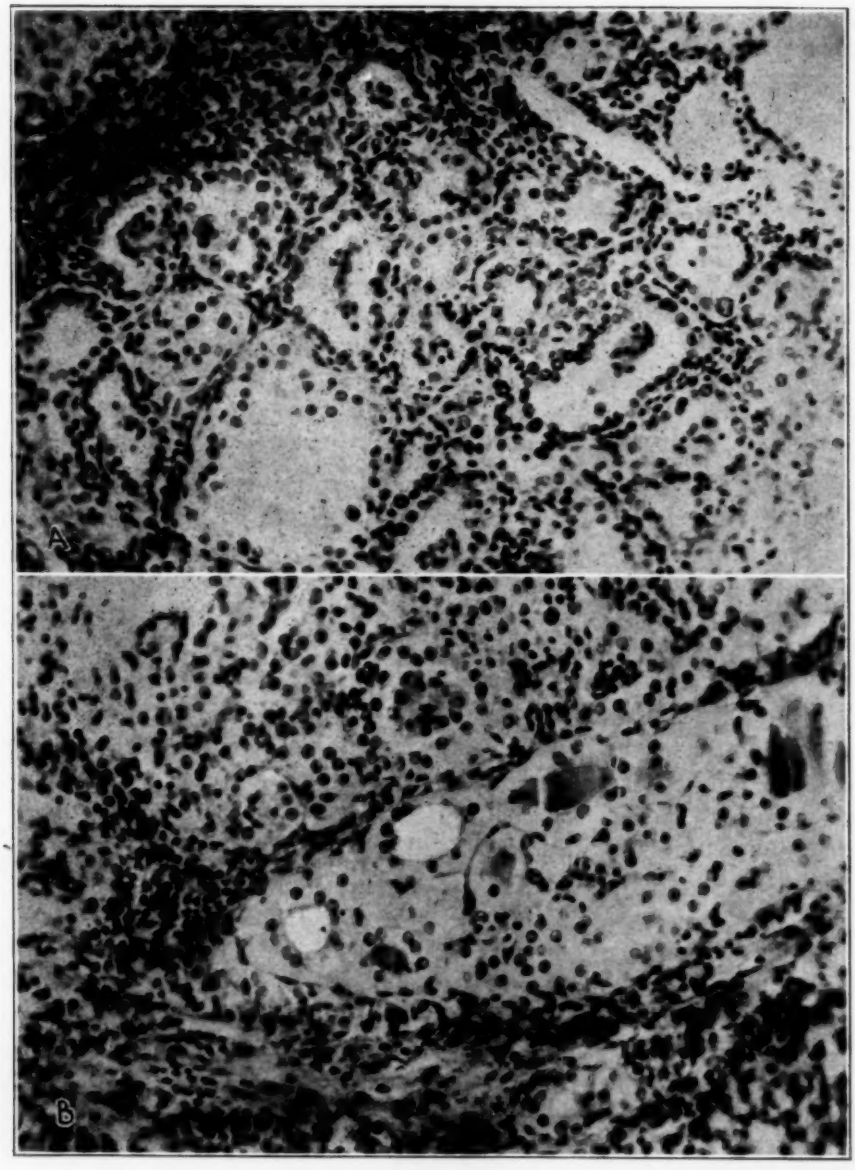


Fig. 2.—*A*, small acini without colloid. Some cells in the lumens. No degeneration of epithelium. *B*, compensatory proliferation of large pale oxyphilic cells identical with Hürthle cells.

majority of investigators (Reist,[8] Graham[2] and Schilling[5]) described them as inactive or degenerated. Hertzler[9] ascribed a pathologic secretion responsible for myxedema to cells of this type, and he advised total thyroidectomy to get rid of these "myxedema cells."

The pale eosinophilic cells with abundant cytoplasm, so characteristic of lymphadenoid goiter, are without doubt identical with the "protoplasm rich" cells of Hürthle.[10] In 1894 Hürthle described them in normal human thyroids on the outer wall of follicles and stated the belief that they were immature reserve cells.

While Hürthle[10] himself did not observe any thyroid tumors composed of this type of cell, about 23 cases of benign and malignant Hürthle cell tumors have been reported since 1907 (Morrow[11]). It is of significance that with few exceptions these tumors occurred in women older than 40 years. The average age of the patients with Hürthle cell tumors reported in the literature is 45.7 years, while the average age of our patients with lymphadenoid goiter is 44.7 years. Two of the lymphadenoid goiters in our series, from women of 36 and 46 years, had small adenomas composed of Hürthle cells, and the tumor cells were of the same form, size and color as the large pale cells in the diffuse tissue of the same specimen.

There is disagreement in the literature regarding the origin of the Hürthle cells. While Getzowa[12] derived them from the postbranchial bodies and Eisenberg and Wallerstein[13] from the parathyroid glands, Wilensky and Kaufman's[14] explanation seems more plausible, stating that the Hürthle cell is a physiologic-pathologic variant of the thyroid cell and that it arises from normal thyroid epithelium because of metabolic or nutritional disturbances.

The fact that Hürthle cells have been found occasionally in normal thyroids of small children (Wegelin[15]) and in exophthalmic goiters

8. Reist, A.: Ueber chronische Thyreoiditis, Frankfurt. Ztschr. f. Path. **28**:141, 1922.

9. Hertzler, A. E.: Surgical Pathology of the Thyroid Gland, Philadelphia, J. B. Lippincott Company, 1936, p. 198.

10. Hürthle, K.: Beiträge zur Kenntnis des Sekretionsvorganges in der Schilddruese, Arch. f. d. ges. Physiol. **56**:1, 1894.

11. Morrow, W. J.: Hürthle Cell Tumor of the Thyroid Gland in an Infant, Arch. Path. **40**:387 (Nov.-Dec.) 1945.

12. Getzowa, S.: Ueber die Glandula parathyroidea, intrathyroidale Zellhaufen derselben und Reste des postbranchialen Koerpers, Virchows Arch. f. path. Anat. **188**:181, 1907.

13. Eisenberg, A. A., and Wallerstein, H.: Hürthle Cell Tumor, Arch. Path. **13**:716 (May) 1932.

14. Wilensky, A. O., and Kaufman, P. A.: Hürthle Cell Tumor of the Thyroid Gland, Surg., Gynec. & Obst. **66**:1, 1938.

15. Wegelin, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8 p. 118.

(Roussy [16]) and that they may give rise to benign or malignant thyroid tumors favors the view that they are young proliferating cells rather than degenerated and atrophic.

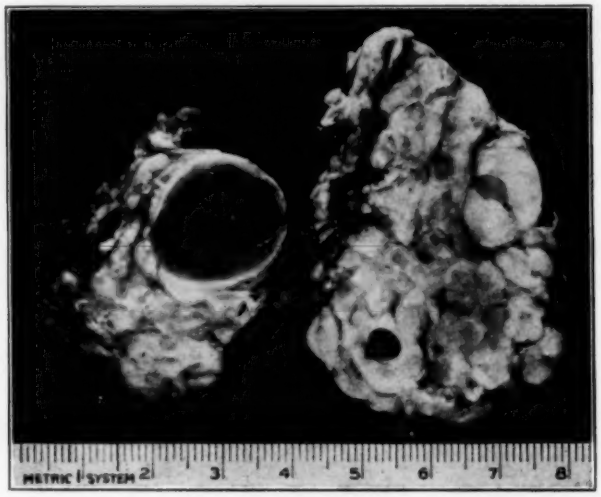


Fig. 3.—Lymphadenoid goiter with adenoma composed of Hürthle cells (case 4).

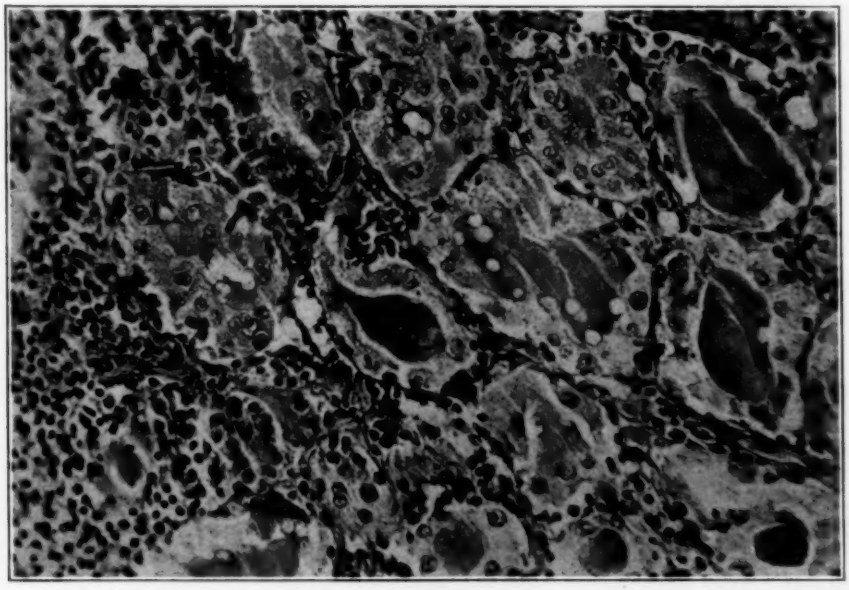


Fig. 4.—Hürthle cells in adenoma, indistinguishable from large pale oxyphilic cells of lymphadenoid goiter (compare with figure 2 *B*).

16. Roussy, G., in Verhandlungsbericht, hrsg. im Auftrag der Schweiz. Internationalen Kopfkonferenz (1933), Bern, H. Huber, 1935, vol. 2, p. 175.

The question that then presents itself is why lymphadenoid goiter in spite of epithelial hyperplasia is often associated with hypothyroidism. To answer it one has to consider the normal activity of the thyroid acinus. Microscopic observations by Williams [17] of the follicle of the living thyroid implanted in transparent chambers have shown that the activity of the thyroid cell is cyclic. The normal cycle consists of two phases: the colloid storage phase and the colloid release phase. During the first phase, which can be precipitated by iodine, the acinar cells actively manufacture colloid and secrete it into the lumen of the follicle, where it is stored. During the release phase, which is under the influence of thyrotropin, the colloid is resorbed from the acinar lumen into the circulation. Normal thyroid function can be maintained only when there is a balance between the two phases of the cycle—colloid secretion and colloid resorption.

Histologic and functional changes in lymphadenoid goiter indicate an interruption of the cycle. The lymphadenoid goiter has lost its faculty to manufacture colloid, and the supply of stored thyroid hormone becomes exhausted. In contradistinction to exophthalmic goiter, which promptly converts into colloid goiter after treatment with strong solution of iodine, U. S. P., even large doses of iodine are unable to restore the manufacture of colloid in lymphadenoid goiter. This explains why iodine has no value in the prevention or cure of lymphadenoid goiter.

The hyperplastic pale cells found in every lymphadenoid goiter of our series represent an attempt to compensate for the exhaustion of thyroid hormone. However, the cells are neither secreting colloid into the acinus nor resorbing it into the blood stream. The oxyphilic secretory material collects in the cytoplasm and distends the cells to a bizarre size.

It is well to remember that in experimental goiter loss of colloid and cellular hyperplasia is also associated with low thyroid function (Hellwig [18]). The recently discovered goitrogenic agent, thiouracil, interferes directly with the synthesis of colloid, as Astwood [19] has shown. By removal of the antagonistic effect of the thyroid secretion on the hypophysis, excessive production of thyrotropic hormone results. The latter stimulates the thyroid to increased colloid resorption and to epithelial hyperplasia, but the basal metabolic rate becomes low because the stored thyroid hormone becomes exhausted and there is no synthesis of colloid. Iodine is unable to restore the normal thyroid cycle, and

17. Williams, R. G.: Microscopic Studies of Living Thyroid Follicles Implanted in Transparent Chambers Installed in the Rabbit's Ear, Am. J. Anat. **62**:1, 1937.

18. Hellwig, C. A.: Experimental Goiter, Arch. Path. **19**:364 (March) 1935.

19. Astwood, E. B.: Treatment of Hyperthyroidism with Thiourea and Thiouracil, J. A. M. A. **122**:78 (May 8) 1943.

administration of thyroxin is necessary to restrain the overactivity of the hypophysis.

A similar sequence of events is apparently the cause of lymphadenoid goiter, except that the thyroid cycle is not interrupted by a chemical agent, as in thiouracil goiter, but by the hyperactivity of the hypophysis following loss of ovarian function. Most lymphadenoid goiters occur in women near or during menopause. A decline of ovarian function removes the antagonistic effect on the activity of the hypophysis and increases its hormone secretion. The excess of thyrotropic hormone will, as in thiouracil goiter, produce in the thyroid loss of colloid and hyperplasia of the thyroid epithelium, but the function of the thyroid will be deficient because there is no synthesis of colloid. Iodine will not restore the normal cycle, and thyroid extract is necessary to counteract the hyperactivity of the hypophysis.

SUMMARY AND CONCLUSIONS

The clinical data and histologic changes in 14 cases of lymphadenoid goiter suggest that lymphadenoid goiter is a clinical and pathologic entity and that it is not an inflammatory process but the result of a disturbance of the normal cycle of thyroid activity—colloid secretion and release.

Two types of epithelial alterations were present in all our cases: (1) small slitlike acini with high cuboid epithelium and loss of colloid and (2) strands of large pale oxyphilic cells which resemble hepatic or adrenal cells. The latter are identical with the so-called Hürthle cells. Hürthle cell tumors occur almost exclusively in women over 40 years of age, as do lymphadenoid goiters. These large pale cells represent in our opinion an attempt to compensate for the exhaustion of colloid in the small slitlike acini.

Lymphadenoid goiter is explained best by a similar sequence of events as occurs in thiouracil goiter except that the disturbance of the cyclic activity of the thyroid acinus is not initiated by a chemical agent but by loss of ovarian function.

ANAPHYLAXIS-LIKE REACTIONS PRODUCED BY ASCARIS EXTRACTS

III. The Role Played by Leukocytes and Platelets in the Genesis of the Shock

M. ROCHA e SILVA, A. PORTO
AND
SYLVIA O. ANDRADE
SAO PAULO, BRAZIL

IN the two preceding papers [1] of this series we have described the main features of the shock produced in the dog by the intravenous injection of deproteinized and dialyzed extracts from Ascaris lumbricoides. We have shown that histamine and heparin are discharged in conspicuous amounts from liver cells when the extracts are injected into the intact animal and that glycogen inhibits this release when injected before the extracts. This effect of liver glycogen was ascribed to its capacity for reducing the number of leukocytes and platelets of circulating blood by allocating them to nonspecified organ structures all over the body. On the contrary, in anaphylactic shock or in the shock produced by Ascaris extracts it should be a preferential allocation of clumped leukocytes and platelets to the structure of the shock organs. As regards the rabbit, pulmonary capillaries have been shown by Dragstedt and co-workers [2] to retain leukocytes during in vitro anaphylactic shock. We have recently shown [3] that liver glycogen produces drastic reductions in the histamine content and the leukocyte and platelet counts in the rabbit and at the same time partially or totally inhibits anaphylactic shock in this species of animal. By dispersing blood elements, glycogen prevents their accumulation in rabbit lung, this apparently being a preliminary condition for development of the shock in this species of animal. As regards the dog, the liver might display similar function during anaphylactic shock, since this organ is mainly concerned in the genesis of the symptoms. There remains no doubt that an initial constriction of suprahepatic veins in the dog constitutes the deflagrating event leading to the anaphylactic shock and

From the Butantan Institute (Porto) and the Department of Biochemistry and Pharmacodynamics, Instituto Biologico (Rocha e Silva and Andrade).

1. Rocha e Silva, M., and Graña, A.: Anaphylaxis-Like Reactions Produced by Ascaris Extracts: I. The Changes in the Histamine Content and the Coagulability of the Blood in Guinea Pigs and in Dogs, Arch. Surg. **52**:523 (May); II. The Mechanism of the Shock Induced in Dogs, ibid. **52**:713 (June) 1946.

2. Dragstedt, C. A.; Arellano, M. R.; Lawton, A. H., and Youmans, G. P.: J. Immunol. **39**:537, 1940.

3. Rocha e Silva, M.; Graña, A., and Porto, A.: To be published.

that the histamine and the heparin which appear in high amounts in the circulating blood and especially in blood in the portal vein are discharged from the liver parenchyma. Since leukocytes and platelets are sharply reduced in peripheral blood during anaphylactic shock, it might be expected that they would be retained in the internal structures of the liver, forming microthrombi, which would contribute to aggravate the circulatory stasis in the portal region. The experiments described in this paper bring direct proofs for this assumption. On the other hand, the fact that a decrease in the leukocyte-platelet count as produced by glycogen partially or totally prevents the discharge of histamine and heparin from liver cells seems to warrant the conclusion that there is a close relationship between this discharge and the accumulation of blood elements to the liver parenchyma. It is important to recall that the perfusion of the liver of sensitized dogs with Tyrode solution or defibrinated blood plus the antigen was unable to produce any appreciable discharge of histamine from liver cells.[1] We have therefore concluded that only the contact of the antigen with the liver cells is not enough to bring forth a liberation of histamine. In the present paper we will show that whole blood has all the constituents which are necessary to bring forth this discharge of histamine and heparin from isolated liver cells when the antigen is added to the system.

MATERIAL AND METHODS

The Ascaris extracts employed were prepared according to the procedure previously described.[1] The anesthetic used was a combination of morphine (10 mg. per kilogram) and liquid dial (Ciba), in the dose of 0.16 cc. per kilogram. In some cases a complement by ether was employed, in others it was deliberately avoided. In a few experiments on perfusion of the liver the animal was simply anesthetized with ether.

The perfusion of the liver was performed in the way previously described, with the difference that the blood (800 cc.) for perfusion was collected over a 3.8 per cent solution of sodium citrate (200 cc.) in a paraffined beaker. All the materials which had to enter into contact with blood were carefully paraffined, with the exclusion of rubber tubings. Before whole blood was added, the liver was perfused with 500 cc. of Tyrode solution (without calcium) to which 20 per cent of the citrate solution was added. In such conditions, leukocytes and platelets were well preserved, even after many passages through the organ. Usually, three or four passages in blank preceded the injection of the Ascaris material into the portal cannula. The velocity of the perfusion was maintained at a high level (150 cc. per minute) during seven or eight passages of the whole blood. Then perfusion stopped, and the retained blood was allowed to drain from the organ. Histamine in the perfusates was estimated on guinea pig ileum both directly before and after extraction by Code's method.[4] The discharge of an anticoagulant (heparin) was roughly estimated by a recalcification of the perfusing blood with tenth-molar solution of calcium chloride and a determination of the clotting time as usual. Platelets were counted according to the method of Fonio, and the

4. Code, C. F.: J. Physiol. **89**:257, 1937.

figures indicate the number of platelets referred to 1 cu. mm. of the starting blood. All the smears intended for counting of platelets were stained with dilute Giemsa stain and observed at a magnification of 900 diameters.

Smears of pieces of liver, in experiments on the intact dog, were uniformly made by immersing an edge of the organ into a shallow dish filled with 3.8 per cent solution of sodium citrate and cutting with sharp scissors a small fragment of liver beneath the surface of the anticoagulant. This procedure was found necessary to avoid spontaneous aggregation of platelets, although it was verified that the aggregates never displayed more than ten or twelve elements packed together. With use of the technic described, the platelets were always uniformly distributed among the erythrocytes when the smears were made by gently rubbing the pieces of liver over microscopic slides. Only occasionally, small aggregates (of seven or ten platelets) could be observed, like those which can be found in a smear from normal blood intended for counting of platelets.

Plasma trypsin (free and total) was estimated according to the method of Iyengar [5] with slight modifications which will be described in a separate paper. All estimations of nonprotein nitrogen were made as usual by the micro-Kjeldahl method.

RESULTS

Identity of the Shock Produced by Ascaris Extracts and Anaphylactic Shock.—Of considerable interest is the question whether the shock developed in the dog by the injection of Ascaris extracts is the consequence of a primary toxic effect of those extracts or of a previous sensitization of the animal to products derived from helminths usually present in their intestinal tract. Many facts are in favor of the latter alternative. Ascaris extracts do not act like a primary toxin, since they are entirely nontoxic for the rabbit and almost so for the cat. Like horse serum in a sensitized animal, they do not liberate histamine from isolated dog liver perfused with Tyrode solution or defibrinated blood, in contrast to the effects produced by snake venom [6] and trypsin.[1] When injected into the unanesthetized dog, Ascaris extracts produce a sequence of symptoms which are common to anaphylactic shock in this species of animal, the only difference being that the symptoms have an extremely severe course. After two to three minutes, the animal presents vomiting, defecation and urination, and seven to ten minutes later it falls in lateral decubitus and stays in this position for fifteen to thirty minutes, entirely unconscious, with the pupils wide open. Frequently, death occurs during this stage; if recovery occurs, the animal shows bloody diarrhea of extreme severity for many hours. At section, the liver is dark and full of blood, the walls of the intestines are hyperemic and the lumen is filled with dark blood. Table 1 shows the condensed protocols of the experiments made on 7 dogs which received decreasing doses of the extracts.

5. Iyengar, N. K.; Sehra, K. B., and Mukerji, B.: Indian M. Gaz. **77**:348, 1942.

6. Feldberg, W., and Kellaway, C. H.: J. Physiol. **90**:257, 1937.

The analogy between the symptoms induced in the dog by the Ascaris extracts and those characterizing anaphylactic shock in this species of animal is so profound that one is induced to apply the observations concerning the mechanism of the former to a better understanding of the latter. It seems to us that many of the conclusions emerging from the study of the shock by Ascaris were rendered clearer on account of the fact that all details are somewhat magnified through the severity of the symptoms.

TABLE 1.—*Shock Produced in Unanesthetized Dogs by Ascaris Extracts*

Dog	Weight of Dog, Kg.	Dose of Extract Injected, Cc./Kg.	Symptoms Observed *
53	11	1.2	2 to 4 min. later: vomiting, defecation, dyspnea; 6 to 25 min. later: prostration, unconsciousness; 45 min. later: bloody diarrhea continuing until 4 hr. later; recovery
55	11	1.2	Half minute later: vomiting; 1 to 4 min. later: urination, prostration, defecation; 20 min. later: agonic agitation; 25 min. later: death. Section: enlargement of the liver, enormous hyperemia of abdominal organs, hemorrhages to the intestinal lumen
60	6	0.8	1 min. later: vomiting; 5 min. later: lateral decubitus, apathy; 7 min. later: prostration, defecation, pupillary dilatation; 8 to 10 min. later: prostration, filiform pulse; 35 min. later: first signs of recovery; 68 min. later: bloody diarrhea; 170 min. later: liquid bloody feces, still prostrated; died overnight
56	15	0.6	1 min. later: vomiting; 4 min. later: defecation, dyspnea; 10 min. later: prostration in lateral decubitus; 15 min. later: restlessness; 23 min. later: elimination of urine; 27 min. later: agonic agitation; 32 min. later: death. Section: enormous enlargement of the liver, hyperemia of abdominal organs, mucus and blood at the lumen of the intestines
62	8	0.5	2 min. later: defecation, vomiting, urination; 7 min. later: prostration in lateral decubitus; 27 min. later: restlessness; 34 min. later: bloody diarrhea; 1 hr. later: complete recovery
57	13	0.4	3 min. later: dyspnea; 10 min. later: somnolence in lateral decubitus; 25 min. later: somnolence; 1 hr. later: recovery; slight bloody diarrhea
65	7	0.4	3 min. later: urination, defecation; 4 min. later: prostration; 8 min. later: defecation; 30 min. later: total recovery

* Time is indicated in minutes after the injection of the extracts.

Perfusion of Liver with Total Citrated Blood.—In 10 dogs we performed the perfusion of the isolated liver with total citrated blood. The amount of citrate used varied from 25 to 20 per cent. It is apparent (table 2) that in all cases there was a definite retention of leukocytes and platelets by the perfused organ. The decrease in the leukocyte and the platelet counts in the perfusates was in most cases sharp enough to be correlated with the injection of the Ascaris material into the portal cannula (fig. 1). As a rule, after stoppage of the perfusion, the blood drained from the organ was collected and the leukocytes and platelets counted again. In some cases, especially in those in which there was no appreciable release of active substances, there was considerable increase of leukocytes and platelets in the drainage fluid but the counting was somewhat difficult since the blood elements were agglutinated.

In 1 case (dog 68) the platelets were found in enormous quantity (up to 1,000,000 per cubic millimeter) in the drainage fluid, and the leukocytes increased from a minimum of 1,750, attained at the sixth passage, to 5,650, in the fluid at drainage. In another case (dog 66), the platelets increased from a minimum of 50,000, at the sixth passage, to 161,000, attained after stoppage of the perfusion, and the leukocytes from 750 to 4,900, in the same circumstances. In all those cases, the platelets appeared to form conspicuous aggregates in the Giemsa-stained smears of the drainage fluid. In the case (dog 67) in which there was considerable increase in histamine and heparin in the perfusates fig. 1*A*), the number of the platelets in the drainage blood remained low (62,000).

Although the histamine was regularly released and found in a free form in the drainage fluid and especially when the liver was excised

TABLE 2.—*Experimental Perfusion of the Liver with Total Citrated Blood; Changes in Histamine and Leukocyte-Platelets After the Injection of Ascaris Extracts*

Dog	Histamine, Micrograms/1 Cc.			Leukocytes ($\times 10^3$)		Platelets ($\times 10^3$)	
	Before	After	Drainage	Before	After	Before	After
48	0.09	0.07	0.15	3.1	0.5	523.0	158.0
65	0.03	0.07	0.33	5.3	1.6	.....	.....
66	0.05	0.10	0.12	4.7	0.4	220.0	47.0
67	0.07	0.61	0.16	6.0	0.4	215.0	60.5
68	0.0	0.02	0.13	3.0	1.7	445.0	186.0
69	0.01	0.03	0.06	9.6	1.2	843.0	390.0
70	0.0	0.05	0.15	5.1	0.6	225.0	23.7
71	0.08	0.06	0.26	3.1	1.1	409.0	29.8
72	0.01	0.05	0.12	3.4	0.1	445.0	80.0
77	0.09	0.16	0.22	5.9	2.7	350.0	78.0

with a sharp knife, the amounts liberated were not in most cases so conspicuous as it appears in vivo after the injection of the Ascaris extracts into the veins of the intact animal. This might be due to either of the following reasons: (*a*) the addition of the anticoagulant (sodium citrate) would protect the aggregates of platelets in such a way that their distintegration is only partial; (*b*) the in vivo conditions are difficult to duplicate in experiments of perfusion. In 1 case (dog 67), however, the discharge of histamine and heparin was especially conspicuous and of the order of magnitude as it occurs in vivo. This definitely proves that intact blood contains all the factors which are necessary to bring forth a discharge of histamine and heparin from liver cells when the antigen is injected.

Retention and Lysis of Platelets in the Liver of Intact Dogs Receiving the Ascaris Extract.—The perfusion experiments described have shown that the vessels of the liver might work as a filter for clumped leukocytes and platelets after the injection of the Ascaris material into the portal cannula. There was clear indication that platelets

formed aggregates that could be found in the drainage fluid after stoppage of the perfusion. In a few cases, a fragment of the perfused liver was cut with a knife directly into a 3.8 per cent solution of sodium citrate and smears made for microscopic examination. Enormous

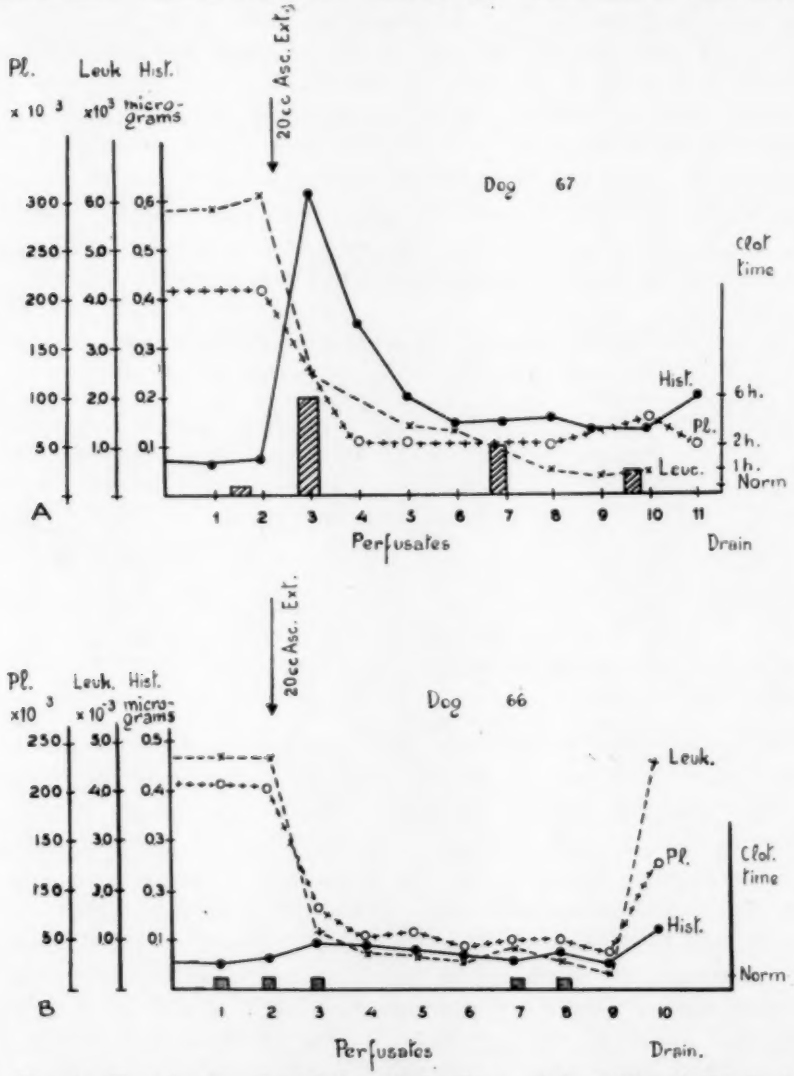


Fig. 1.—Experiments of perfusion of the livers of dogs 66 and 67. In both cases there was a sharp reduction in leukocytes and platelets in the perfusates immediately after the injection of the extract. Note the correlation between the retention of blood elements and the discharge of active substances (dog 67).

aggregates, of 20 or more platelets, were found all over the slide. This fact is an indication that those aggregates were probably protected by the anticoagulant used in the perfusing experiments.

In another series of experiments we have tried to get a proof of a similar retention of platelets by the liver of the intact animal. The animals were anesthetized with morphine plus dial and the blood pressure of the carotid artery recorded. Before the injection the abdomen was opened and a piece of the liver cut directly into a 3.8 per cent solution of sodium citrate. The piece of the liver was rapidly freed of the excess of bloody fluid and carefully rubbed over a microscope slide. By use of the technic described, the platelets were found almost uniformly distributed all over the smears (fig. 2 *a*). Besides rare

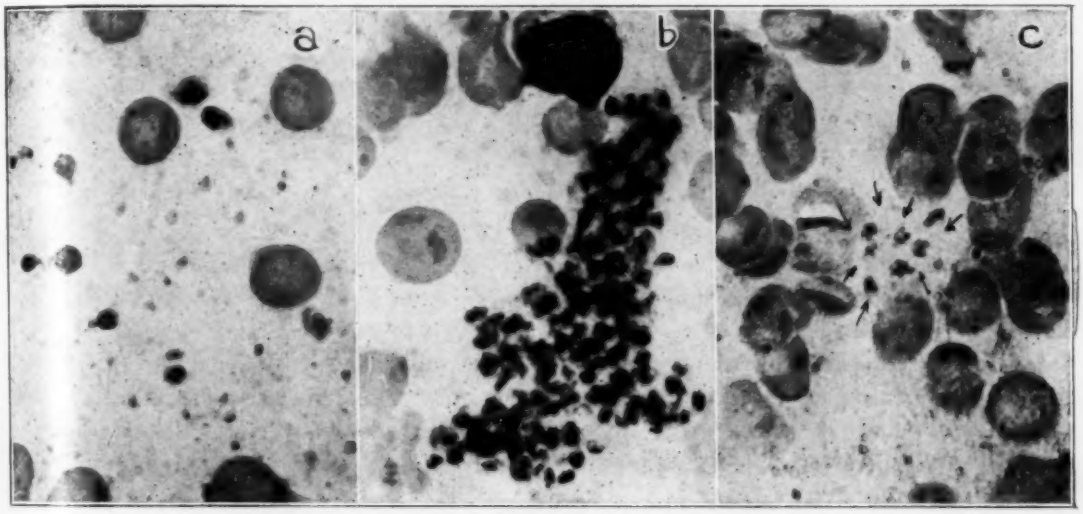


Fig. 2.—Giemsa-stained smears from pieces of dog liver, before (*a*), immediately after (*b*) and ten minutes after (*c*) the injection of Ascaris extract. The animal died in fifteen minutes, showing enormous increases in blood hisamine and heparin. The aggregates seen in the second slide are disintegrated and vanishing in the last smears. Note the change of colorability of the platelets in *c*. × 1,077.

leukocytes, there were many large endothelial cells, probably originating in the liver capillaries. One to two minutes after the injection of the Ascaris material, another fragment of the liver was taken, in absolutely identical circumstances. Since the organ was found enormously swollen by that time, the collecting of a small piece of the organ was rather easily performed. In most of the cases, the smears obtained from this second piece of liver show enormous aggregates of platelets (over 100 platelets clumped in a single mass) scattered over the slide (fig. 2 *b*) but mostly around the mentioned endothelial cells. In the most favorable cases, hundreds of those aggregates can be found in a single smear, and if one tries to count the platelets it becomes clear that most of them belong to aggregates and only a few are uniformly distributed among the erythrocytes.

In the smears obtained from the pieces of liver taken many minutes after the shock there was a definite decrease both in the size (fig. 2 *c*) and in the number of the aggregates, this being good evidence that the earlier aggregates have been dissolved during the reaction. We cannot admit that the platelets returned to the general circulation, since the animal died in fifteen minutes, without recovery, and the liver became more and more engorged with blood. Besides that, the counting of platelets in the blood collected in the femoral vein did show a lasting decrease, almost to zero, of those elements. It seems logical to conclude that the aggregates of platelets disintegrated during the shock. This was definitely suggested by the observation of the smears from pieces of liver taken two, five and ten minutes after the injection of the Ascaris material. Although the aggregates of platelets had a bright appearance in the first smears, they somewhat changed their colorability in the later stages of the shock, and in the last smears they showed only scarce eosinophil granules at the places where there should have been aggregates of platelets.

Plasma Trypsin During the Shock.—Plasma trypsin has been studied in the human being mainly in connection with clinical events. There is no detailed study of the variations of this enzyme under several morbid conditions experimentally induced in animals. As intact blood seems to carry most of the factors which are necessary for the discharge of histamine and heparin from dog liver during anaphylactic shock, it seemed to us advisable to study plasma trypsin during the different phases of the shock in an attempt to verify whether activation of this enzyme might be the final step in the mechanism of discharge of those active substances.

As shown by Schmitz [7] and Iyengar and co-workers,[5] trypsin is found in the plasma in bound and "free" forms. Free trypsin can be estimated after precipitation of plasma with 10 volumes of acetone, while total trypsin is estimated after precipitation of the plasma with 2.5 per cent trichloroacetic acid solution. Although the detailed description of the technic employed and the results already obtained under several experimental conditions will constitute the object of a separate paper, it seems convenient to present here a few typical experiments concerning the problem under study. Table 3 shows the results obtained in experiments on liver perfusion of 6 dogs. It appears clear that, although some increase of free trypsin was consistently observed, there was a definite reduction of it when the samples were collected at the height of the reaction. In the case of the isolated liver of dog 67, in which there was a considerable release of histamine and heparin, this

7. Schmitz, A.: Ztschr. f. physiol. Chem. **250**:37, 1937.

was clearly observed in the third perfusate, coinciding with the peak of histamine and heparin. Also the reduction of free trypsin was more apparent in the drainage fluid, in which the amounts of active substances increased. The correlation between this decrease in free trypsin and the appearance of heparin in the perfusates is suggested also by similar observations obtained in the intact dog and also by the fact, which we have verified, that heparin when added to plasma definitely reduces the proteolytic activity of free trypsin and, in a much less extent, of total trypsin. It also became clear that some trypsin is retained by the liver submitted to the perfusion, but in some cases definite increases in total trypsin were observed, not only in perfusion experiments but also in the intact animal, as shown in table 4.

TABLE 3.—*Total and Free Trypsin in the Plasma of Perfusates Taken at Different Stages of the Perfusion* *

Dog	Perfusates	Plasma Trypsin (Mg. NPN/100 Cc.) Total	Free	Dog	Perfusates	Plasma Trypsin (Mg. NPN/100 Cc.) Total	Free
66	1st, before	74.0	3.5	69	1st, before	57.5	1.0
	9th, after	32.2	8.6		3d. after	64.0	21.0
	12th, after	33.5	30.5		Drainage	59.0	0.0
67	1st, before	97.0	60.0	70	1st, before	66.0	24.0
	3d, after	86.0	1.5		7th, after	71.0	19.5
	8th, after	99.5	100.0		Drainage	71.0	27.0
68	1st, before	122.0	59.0	71	1st, before	72.5	48.7
	7th, after	214.0	134.0		7th, after	32.0	33.0
	Drainage	168.0	1.5		Drainage	32.0	33.0

* All figures indicate the amount of nonprotein nitrogen per hundred cubic centimeters of plasma after an incubation of forty-eight hours, at 38 to 39 C. Before and after refer to the moment of the injection of the ascaris extract into the portal cannula. The dog numbers compare with those given in table 2.

In 8 anesthetized dogs we have estimated total and free trypsin in oxalated plasmas collected at several stages of the shock. It is apparent (table 4) that the same reduction in free trypsin was observed in most of the cases, especially in those in which the shock had been particularly severe, with considerable increases in blood histamine and appearance of anticoagulant in the circulating blood. In those cases, the increases in total trypsin were more steady and in a few cases significant. In the cases of dogs 84, 85 and 86 we have explored the latent period in an attempt to catch the initial changes of trypsin in the samples of blood collected in the portal vein. This procedure was rather to be condemned since the handling of abdominal organs during the start of the shock somewhat reduced the severity and rendered it slower in its development, as verified in separate experiments. But even when blood from the portal vein was collected as soon as one or two minutes after the injection we observed in 2 cases a decrease and only in 1

case (dog 86) a significant increase in free trypsin. In the latter case the shock was exceptionally mild, without increase in histamine in the blood and with slight increase in blood incoagulability.

TABLE 4.—*Estimations of Plasma Trypsin (Total and Free) During the Shock Produced by Ascaris Extracts in Intact Dogs* *

Dog	Blood Samples	Plasma Trypsin (Mg. NPN/100 Cc.) Total	Free	Intensity of Shock
43	Before	72.5	....	+
	13 min. after	69.5	....	
47	Before	94.0	43.2	++++
	12 min. after	111.5	33.2	
	18 min. after PV	26.1	14.6	
50	Before	94.0	44.0	++++
	13 min. after	92.0	4.0	
	16 min. after PV	80.0	8.0	
	39 min. after PV	112.0	52.0	
51	Before	152.0	87.0	++++
	8 min. after	104.0	16.0	
	13 min. after PV	100.0	15.0	
	21 min. after	120.0	12.0	
74	Before	128.0	36.0	++
	10 min. after	117.2	31.2	
	30 min after	55.4	3.2	
84	Before	136.4	37.0	++++
	2 min. after PV	143.4	31.0	
	4 min. after PV	162.6	32.6	
	16 min. after PV	150.3	26.9	
	18 min. after	132.2	15.0	
85	Before	105.8	28.8	++
	1 min. after PV	85.6	14.4	
	8 min. after PV	135.5	26.4	
	15 min. after PV	137.5	30.8	
86	Before	105.0	13.1	+
	2 min. after PV	100.0	23.0	
	12 min. after PV	110.0	16.3	
	29 min. after	88.8	....	

* The samples collected at the trunk of the portal vein are marked PV. The intensities of the shock mean: +, mild shock, with prompt recovery in less than ten minutes; ++, more prolonged fall of the carotid blood pressure, but recovery occurring in more than fifteen to twenty minutes (usually there were small increases in blood histamine and moderate changes in the coagulability of the blood); +++, fatal shock, death occurring by secondary shock, two or three hours later; ++++, death in less than twenty minutes. The figures indicate the increases in nonprotein nitrogen per hundred cubic centimeters of plasma, after an incubation period of forty-eight hours at 38 to 39 C.

COMMENT

Considerable work has been done in the past to show the participation of leukocytes and platelets in the genesis of anaphylactic shock,[8] and many persons have attempted to show that a decrease in the white

8. Andrewes, F. W.: Lancet **2**:8, 1910. Widal, F.; Abrami, P., and Brissaud, E.: Presse méd. **28**:181, 1920. Webb, R. A.: J. Path. & Bact. **27**:79, 1924. Achard, C., and Aynaud, M.: Compt. rend. Soc. de biol. **67**:83, 1909. Kopeloff, N., and Kopeloff, L. M.: J. Immunol. **40**:471, 1941.

blood elements (hemoclastic shock) would be the most important event in anaphylaxis. The fact that an entirely nontoxic substance, such as liver glycogen, can produce enormous decrease in leukocytes and platelets without shock proves that leukopenia and thrombopenia alone cannot explain the genesis of anaphylactic shock. In the second report of this series, we postulated a connection between the decrease in the platelet and leukocyte counts and the discharge of pharmacologically active substances from dogs' liver, on the basis of the finding that glycogen prevents this discharge when previously injected into the animal. We have also assumed that a mechanical obstruction of liver capillaries with clumped white blood elements might be the initial condition leading to the liver stasis and the discharge of histamine and heparin. In certain cases this mechanical obstruction without much histamine and heparin in the blood appeared to constitute the most important etiologic factor for the production of the shock. In the foregoing paper we adduced proofs for this retention of leukocytes and platelets by the liver, not only in vitro (perfusion experiments) but also in the intact animal. The correlation between the discharge of histamine and heparin and the retention of the leukocytes and the platelets by the isolated liver was also strongly suggested by those experiments. In the intact animal we have observed that the enormous aggregates of platelets which are found in smears of pieces of the liver taken immediately after the drop of blood pressure in the carotid artery disappear or become highly altered six to ten minutes after the shock, this being a clear indication that the aggregates of platelets are lysed or otherwise disintegrated during the shock.

There still is a gap to be filled in this chain of events leading to the discharge of histamine and heparin. As shown before,[9] histamine is promptly released by the interaction of proteolytic enzymes. When one considers the rapidity of the discharge of free histamine by trypsin as verified in perfusion experiments on dog liver or guinea pig lung it seems logical to conclude that the histamine must be linked to the end of the amino acid chains constituting normal cell proteins. The specificity of this linkage is of the arginine-amide or lysine-amide type, as shown before.[10] This linkage can be specifically ruptured by trypsin. On the other hand, we have proofs that trypsin also releases heparin. This was shown by estimating heparin in the blood of intact dogs submitted to trypsin shock[11] and also by direct experiments on perfusion of the liver with crystalline trypsin. Besides histamine, there was a release of an anticoagulant that might be tested in the boiled perfusates,

9. Rocha e Silva, M.: Arch. f. exper. Path. u. Pharmakol. **194**:335, 1940.

10. Rocha e Silva, M., and Andrade, S. O.: J. Biol. Chem. **149**:9, 1943.

11. Rocha e Silva, M., and Dragstedt, C. A.: Proc. Soc. Exper. Biol. & Med. **48**:152, 1941.

therefore after destruction of the trypsin. Since trypsin releases also adenyl compounds and a slowly reacting substance, as shown by Trethewie,[12] it remains clear that the type of injury produced by trypsin is of the same kind as that produced by anaphylaxis. This analogy was repeatedly emphasized by us [13] and also by Feldberg [14] and Dragstedt and Wells.[15]

The first question that arises is to know which trypsin is the agent concerned in the reaction. Since intact dogs' blood is necessary for the reaction leading to the release of histamine and heparin one is

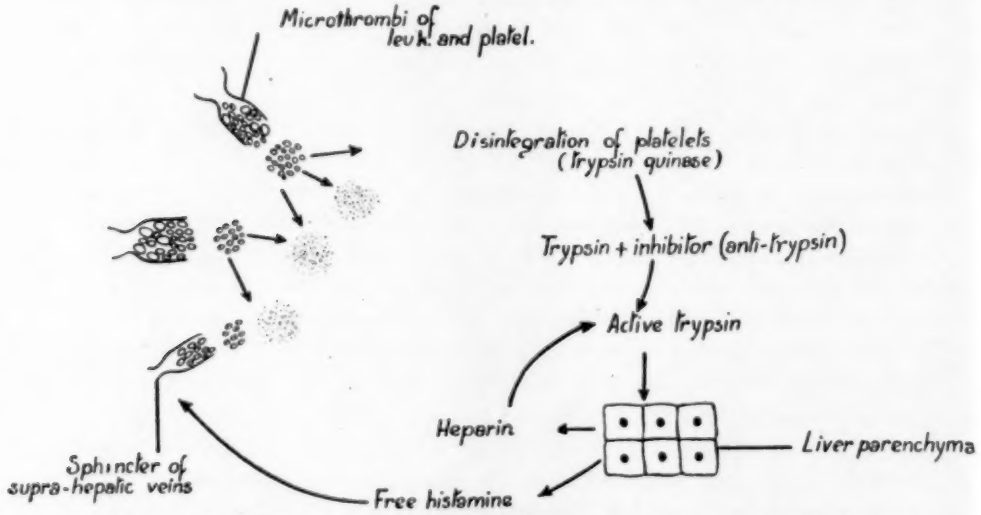


Fig. 3.—Probable chain of reactions leading to the discharge of histamine and heparin from dog liver parenchyma during anaphylactic shock.

bound to take into consideration the possibility of an activation of plasma trypsin as the ultimate mediator for this release from dogs' liver. As shown by Iyengar [16] and confirmed in our laboratory, platelets contain a trypsin quinase which ruptures the combination of trypsin with the inhibitor (antitrypsin). Therefore, if platelets are clumped and lysed in the liver capillaries, it becomes clear that activation of plasma trypsin might be the final step leading to a discharge of histamine and heparin. The scheme of figure 3 was drawn to visualize those probable interrelationships.

12. Trethewie, E. R.: Australian J. Exper. Biol. & M. Sc. **20**:49, 1942.

13. Rocha e Silva, M.: J. Allergy **15**:399, 1944; footnote 9.

14. Feldberg, W., in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 3, p. 671.

15. Dragstedt, C. A., and Wells, J. A.: Quart. Bull. Northwestern Univ. M. School **18**:104, 1944.

16. Iyengar, N. K.: Proc. Indian Acad. Sc., Sect. B **15**:106 and 123, 1942.

The final proof for this theory would be the demonstration that the complex trypsin plus inhibitor is split during the shock. We have made many estimations of free and total trypsin before and after the onset of the shock. At the same time, histamine was estimated in the blood and the discharge of an anticoagulant was roughly verified. In such cases in which the shock was maximal and the discharge of histamine and heparin conspicuous, there was drastic reduction of free trypsin, although total trypsin was unchanged or definitely increased. This diminution of free trypsin at the height of the shock can be attributed to the release of heparin. There is considerable work done to show the antitryptic action of heparin.[17] More recently, Wells and co-workers [18] were unable to demonstrate any antitryptic effect by heparin, using hemoglobin as a substrate. The differences in the substrates used might explain the contradictory results referred to previously. In the case of plasma trypsin, we have found a definite antagonizing effect by heparin when tested on free trypsin. When total plasma trypsin was made free by a precipitation with dilute trichloracetic acid (2.5 per cent solution) heparin no longer displayed antitryptic action. It seems that the plasma contains a factor that complements the antitryptic effect of heparin. This factor would remain in solution after precipitation of trypsin plus substrate by trichloroacetic acid. Whether this factor can be identified with the heparin complement found by others [19] in the blood is a question requiring further experimentation.

All the facts considered, it seems rather difficult to put into evidence any activation of tryptic agents during anaphylactic shock in the dog. The discharge of histamine and heparin by trypsin is so sudden that there is no way of detecting the enzyme in a free form, since the discharge of heparin will instantaneously blockade its enzymatic activity. This might explain the failure of Dragstedt and Wells [18] and of us to show any increase of free trypsin during anaphylactic shock. Other systems which are being studied in our laboratory might be more successfully used to test the final implications of the theory advanced.

Remaining also obscure is the origin of the extraproteolytic activity appearing in the plasma after the injection of the Ascaris extracts, both

17. Horwitt, M. K.: Science **92**:89, 1940. Glazco, A. J., and Ferguson, J. H.: Proc. Soc. Exper. Biol. & Med. **45**:43, 1940.

18. Wells, J. A.; Dragstedt, C. A.; Cooper, J. A., and Morris, H. C.: Proc. Soc. Exper. Biol. & Med. **58**:57, 1945.

19. Quick, A J.: Proc. Soc. Exper. Biol. & Med. **35**:391, 1936. Ziff, M., and Chargaff, E.: J. Biol. Chem. **136**:689, 1940.

in vivo and in vitro (perfusion experiments). Since part of the trypsin might be retained in the organ, it appears probable that the increases would be even more conspicuous than those actually determined. The disintegration of blood elements might provide for some of this extra trypsin, but we must also consider the possibility of a release of proteolytic enzymes from the liver parenchyma itself, as shown by Rawlinson and Kellaway [20] to occur in certain forms of injury to the cells.

SUMMARY

Experiments made on the unanesthetized dog have shown the close similarity between the symptoms characterizing the shock produced by Ascaris extracts and those which are peculiar to anaphylactic shock. When all the results presented in this and the two preceding papers of this series are summed up, it seems logical to conclude that the two types of shock have the same mechanism.

When the isolated dog liver is perfused with citrated whole blood contained in paraffined receptacles, a conspicuous decrease in leukocytes and platelets follows the injection of Ascaris extracts into the cannula. In most of the cases, small amounts of histamine and of an anticoagulant (heparin) are released to the perfusing blood, and in 1 case considerable amounts of both were discharged from the perfused liver. This definitely shows that intact blood contains the factors which are necessary to produce a release of histamine and heparin from liver cells when the extract is added.

In microscopic examinations of smears made from pieces of the liver taken before and after the shock in the intact unanesthetized animal, platelets are found forming enormous aggregates which disappear or partially disintegrate during the later stages of the shock.

Plasma trypsin (free and total) was estimated in the blood used for perfusion of the liver before and after the injection of the Ascaris extracts. Similar determinations were made in the circulating blood of the intact animal given Ascaris extracts intravenously. Although in a few cases there was a clear indication of an activation of plasma trypsin, in most of the cases, especially when the blood was collected at the height of the shock, there occurred a definite decrease in free trypsin. This diminution in free trypsin was ascribed to the appearance of heparin in the circulating blood.

---

20. Rawlinson, W. A., and Kellaway, C. H.: Australian J. Exper. Biol. & M. Sc. **22**:69, 1944.

An attempt to understand the mechanism of anaphylactic shock in the dog was made on the basis of the obvious correlation between the discharge of histamine and heparin and the clumping and disintegration of blood elements, especially platelets, occurring inside the liver capillaries.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

FRANK HINMAN, M.D.
SAN FRANCISCO

ALEXANDER B. HEPLER, M.D.
SEATTLE

ROBERT GUTIERREZ, M.D.
NEW YORK

GERSHOM J. THOMPSON, M.D.
AND
EDWARD N. COOK, M.D.
ROCHESTER, MINN.
AND
VINCENT J. O'CONOR, M.D.
CHICAGO

KIDNEY

Stone.—Boyd [1] states that in operations for stones in the kidney one of the important duties of the surgeon is prevention of recurrence of stones by removal of all existing causes of formation of stones and by employment of an operative technic in which damage to the renal substance is limited to that which is absolutely necessary. It is necessary for the surgeon to have (1) a knowledge of the normal circulation in the kidney and of the variations which are by no means infrequent and (2) to know the conditions which are generally accepted as being the cause of or predisposing to the formation of stones. Briefly, these can be placed under four headings: (1) precipitation of urinary salts in the calices and pelves, (2) lack of free drainage from the kidney, or so-called urinary stasis, (3) injury to the mucous lining of the calices and pelves and (4) urinary infection with bacteria, which leads to urinary decomposition and damage to the mucosa. Rarely are stones caused by any single factor.

At nephrolithotomy the incision through renal substance should be made at the point where the arterial circulation of the kidney divides. Unobstructed postoperative drainage of urine is often best obtained by a nephrostomy tube, and whenever an infected kidney is opened prolonged drainage of the wound in the abdominal wall by means of rubber tubing will prevent closure of the abdominal wall before the deeper, more cellular parts of the wound have healed and expelled any infection.

1. Boyd, M. L.: Kidney Operations in Renal Calculus, South. M. J. **36:** 723-731 (Nov.) 1943.

Hamer and Mertz [2] discuss disappearance of renal calculi following employment of solution G, a solution of citric acid, magnesium oxide and sodium carbonate of p_H 4. The patient was a woman who had alkaline renal calculi which had been present since pyelolithotomy had been performed three years previously. The principal stony mass was removed at a second pyelolithotomy, and several clusters of calculi which were not removed at this operation were dissolved by the persistent use of solution G. Ten months after the patient was dismissed from the hospital renal function was improved and roentgenologic examination revealed no shadow of a stone.

Scholl,[3] in discussing this paper by Hamer and Mertz, states that he was not so fortunate as they in dissolving a stone in 1 case. The patient was a woman 20 years old who had a small stone in a single remaining kidney. Because she had had a difficult time when the right kidney was removed, she refused operation. She had one episode of ureteral obstruction on the left side which was relieved by the pushing of the stone back to the renal pelvis, insertion of a ureteral catheter and injection of solution G by the continuous drip method. The stone could not be seen on roentgenologic examination, and it was thought that the stone had disappeared but three months later, when roentgenologic examination was performed, the stone was observed again. The ureteral catheter was reinserted, and continuous irrigation was carried out for five days, after which the stone again disappeared from the roentgenogram. Four months later, it was reforming. Apparently the matrix of the stone remained, but all the shadow-casting substance was dissolved.

Keyser,[4] in discussing the paper of Hamer and Mertz, states that his interest in the problem goes back to 1932, when he was able to dissolve a recurrent phosphate stone almost completely by urinary acidification by means of an acid diet and by administration of dilute nitrohydrochloric acid by mouth and as an irrigant through indwelling catheters. After this, further well known efforts were made by him and others. The use of acid-ash diets, vitamin A, citrate and buffered citrate solutions, such as solution G, of Suby, was sponsored by their several proponents. Each of these in turn was applied at times, with seeming success. However, on the whole, the use of measures for dissolution

2. Hamer, H. G., and Mertz, H. O.: Disappearance of Renal Calculi Following the Employment of Solution G: Report of a Case, Tr. Am. A. Genito-Urin. Surgeons **37**:115-121, 1944.

3. Scholl, A. J., in discussion on papers of Foulds,[5] Hamer and Mertz,[2] Bugbee, Bumpus and Braasch and Goyanna,[13] Tr. Am. A. Genito-Urin. Surgeons **37**:147-148, 1944.

4. Keyser, L. D., in discussion on papers of Foulds,[5] Hamer and Mertz,[2] Bugbee, Bumpus and Braasch and Goyanna,[13] Tr. Am. A. Genito-Urin. Surgeons **37**:150-152, 1944.

was disappointing. Hegar several years ago suggested that the softer elements of recurrent concrements are dissolved and that the dense, hard calculi, which stand out so strikingly in roentgenograms, remain most resistant.

In the past three years a study of dissolution of stones in vitro has been made by physical chemists at the Virginia Polytechnic Institute. Scherer and Claffey, of this institution, in collaboration with Keyser analyzed several hundred urinary calculi. These were placed in an especially constructed continuous irrigator with thermostatic control. The gamut of solvents was run. They found that solution G (the citrate-magnesium solution of Suby) was probably the best of the solvents. However, its effect was not always striking, especially when oxalate or urate was in preponderance. To a greater degree, the density and crystalline nature of the stone seemed to affect its solubility. Keyser found that preliminary application of enzymes would definitely accelerate the rate of dissolution of these stones when the solvent was applied to them in vitro. Of these enzymes, 0.5 per cent solution of urease, if applied for a short time, would increase the disintegration of the stone when it was subjected subsequently to the action of solution G in the irrigator. This was especially true when alkaline earth calculi were used. The action of this enzyme seems to be related to its effect on the colloid framework of the stone. If the calculus was ground to powder and this powder dissolved in solution G, its organic and mineral components would be separated by dialysis. When the organic matter thus separated was treated with a solution of urease at 38 C. for six hours, the mass would swell to five hundred times its original volume. Thus the action of this enzyme, urease, seems to be one of causing a swelling of the organic matter in the stone. This, in consequence, increases the surface action between the crystalline matter of the calculus and the ions of the solvent.

The use of these irrigating solutions as solvents is disappointing when stones are dense. The solutions are useful, however, in dealing with small, softer recurrences, especially in the bladder, where tidal irrigation may be used. In the bladder softer alkaline stones, incrustations on tumors or ulcers and incrusted cystitis may be treated with reasonable hope of success. The work done with urease and other enzymes in the test tube offers hope that better methods of attacking the problem may be devised. As yet it is difficult to apply such treatment without the all too frequent hazard of sharp reactions. Unless the patient tolerates irrigation well and unless after a few days some evidence of dissolution is apparent, it is Keyser's opinion that persistence in such treatment should be avoided.

Foulds [5] reports a case of renal calculi and parathyroid adenoma. Stones had formed in both kidneys in a period of several years when studies of the concentration of calcium and phosphorus in the blood were first made. Though the blood calcium levels were raised significantly, the normal phosphorus level together with the oxalate type of stone and the absence of changes in the bones led Foulds to abandon the diagnosis of hyperparathyroidism. Eight years later, when unmistakable findings were present, such as bilateral renal calculi, pain in the bones, fatigue, weakness, roentgenologic evidence of osteitis fibrosa cystica, elevated levels of blood calcium and decreased levels of blood phosphorus, correct diagnosis was made and proved by operation and pathologic examination of the adenoma, which had been removed.

Keyser,[6] in a discussion of Fould's paper, states that it brings up the interesting relationship between hyperparathyroidism and calculous disease. For some reason hyperparathyroidism does not seem to occur so frequently in the South as in other geographic areas. Keyser has had the opportunity of observing 4 cases in which lithiasis was present. The diagnostic criteria of hyperparathyroidism are not always clearcut. Changes in bones, elevated levels of blood calcium, low levels of blood phosphorus and hyperexcretion of calcium in the urine confirm the diagnosis. In cases in which no changes have occurred in the bones but in which excessive excretion of calcium in the urine, perhaps with low levels of serum phosphorus, low levels of calcium and low levels of serum protein, is found, diagnostic problems arise. Renal insufficiency with retention of calcium may present diagnostic difficulty.

As an example Keyser presents the case of a woman aged 22. Pronounced osteoporosis of the skull, clavicles and long bones was present, and these bones were thinned out almost to paper thickness in certain areas. A huge stone was found in the left ureter, and multiple shadows were observed in the right kidney. A level of calcium of 13 to 15 mg. per hundred cubic centimeters of serum, a level of phosphorus of 2 mg. per hundred cubic centimeters of serum and a urinary excretion of 400 to 500 mg. of calcium on a low calcium diet comprise the typical picture of hyperparathyroid disease. A tumor of the parathyroid, almost the size of a golf ball, was removed. After a stormy postoperative course the patient recovered enough to have the ureteral stone removed. Results of laboratory tests of blood and urine returned to normal limits.

Tuberculosis.—In 19 cases of renal tuberculosis reported by Cibert, Gayet and Mafart,[7] there were twenty-six pregnancies, of which twenty

5. Foulds, G. S.: Renal Calculus with Parathyroid Adenoma, Tr. Am. A. Genito-Urin. Surgeons **37**:109-113, 1944.

6. Keyser,[4] pp. 149-150.

7. Cibert, J.; Gayet, R., and Mafart, Y.: Tuberculose rénale et grossesse, J. d'urol. **52**:62-65 (May-June) 1944.

went to term, three terminated in premature delivery and three in abortion. Deliveries were normal in 2 of 3 cases in which the mothers were suffering from renal tuberculosis; 1 woman had three normal pregnancies after removal of the more involved kidney, although tuberculosis was present in the remaining kidney. Evidence of aggravation of renal tuberculosis during pregnancy was present in only 3 of the cases, but in 7 cases an exacerbation of symptoms followed within a few weeks after delivery. Nephrectomy may sometimes be necessary in the early stage of pregnancy in unilateral renal tuberculosis if severe or moderately severe symptoms are present and especially if cystitis is present. In bilateral renal tuberculosis, when there are urinary symptoms nephrectomy is indicated in early pregnancy if one kidney is involved much more extensively than the other. If both kidneys are much involved and cystitis is severe, therapeutic abortion or premature induction of labor must be considered. The authors were of the opinion that with the modern methods of treatment and care of tuberculous patients cases of severe renal tuberculosis are not encountered so frequently as they formerly were.

In the discussion of this paper, Michon [8] reports 3 cases of unilateral renal tuberculosis in pregnant women; symptoms were mild, and little or no cystitis was present. Pregnancy and delivery were normal, and urinary symptoms were not increased. Nephrectomy has since been performed in 2 of these cases, without complications. In another case of bilateral renal tuberculosis, two normal pregnancies and deliveries occurred; the patient improved definitely under medical treatment, and no evidence of any aggravation of the renal tuberculosis by either pregnancy was found.

Nesbit, Keitzer and Lynn [9] present data on 260 cases of genitourinary tuberculosis in which the patients have been followed for a period of five years or more. It is pointed out that in this series men are affected more frequently than women, in a ratio of about 2:1, and that the urine in about a third of the cases was infected secondarily by organisms other than the tubercle bacillus. In 50.3 per cent of the cases in which nephrectomy was performed the patients were living an average of eleven years after operation, while in 81.3 per cent of the cases in which operation was not performed the patients died in an average of three years. The authors could not state that an accompanying genital complication in men increases the mortality rate in renal

8. Michon, L., in discussion on Cibert, Gayet and Mafart,[7] pp. 85-87.

9. Nesbit, R. M.; Keitzer, W. A., and Lynn, J. M.: The Prognosis of Renal Tuberculosis, Treated by Nephrectomy, and the Outlook of the Patient Who Is Considered Unsuitable for Operative Treatment, J. Urol. **54**:227-234 (Sept.) 1945.

tuberculosis, and they assume that the higher rate among men is due to the higher mortality rate of tuberculosis generally in this group.

Three facts derived from these figures are proved to be statistically significant: 1. In cases in which nephrectomy is performed the survival rate will be lower if acid-fast bacilli are demonstrated (by inoculation of a guinea pig) in the urine from the remaining kidney than it is if the urine from the remaining kidney is normal. 2. In tuberculosis of the urinary tract the period of survival of women is longer than that of men. 3. The mortality rate for genitourinary tuberculosis is adversely influenced by the presence of lesions of the bones, joints or lungs. The operative mortality rate for nephrectomy was 0.88 per cent. The prognosis was bad in tuberculous perinephric abscess; the operative mortality rate was 30 per cent, and 30 per cent of the survivors lived less than one year.

Hydronephrosis.—Servelle [10] reports 6 cases of hydronephrosis and megaloureter. Treatment in 2 consisted in removal of the aorticorenal ganglion on the affected side and in 4 in infiltration or resection of the splanchnic nerve. It was found that removal of the ganglion relieved pain but did not reduce the size of the ureter or of the renal pelvis. In 2 cases resection of the splanchnic nerve was performed; in both, results were good, symptoms were entirely relieved and the size of the renal pelvis and of the ureter was definitely diminished. In 1 case in which the renal pelvis was greatly dilated, preliminary infiltration of the splanchnic nerve during operation (nephropexy) caused a sudden contraction of the renal pelvis. Subsequently resection of the splanchnic nerve was performed on the affected side; symptoms were relieved permanently, and hydronephrosis was diminished more than half. One patient who had bilateral hydronephrosis was treated by infiltration of both splanchnic nerves. Symptoms were relieved, and diminution of the hydronephrosis occurred. Section of the splanchnic nerve was advised, but the patient did not return for this operation. In the sixth case, the patient was pregnant and dilatation of the renal pelvis and ureter was discovered when pyelonephritis developed. Lavage of the pelvis and infiltration of the splanchnic nerves resulted in a complete clearing up of the pyelonephritis and pronounced diminution of the size of the ureter and pelvis. Infiltration of the splanchnic nerves is well tolerated in pregnancy.

On the basis of his results, the author concludes that unilateral hydronephrosis and megaloureter are best treated by resection of the splanchnic nerve, which should be combined with removal of the upper part of the lumbar chain. In certain cases, as in pregnancy or diabetes,

10. Servelle, M.: Traitement neuro-chirurgical de l'hydronéphrose et du megauretère, J. d'urol. **51**:57-67 (May-June) 1943.

infiltration of the splanchnic nerve is sufficient. If hydronephrosis and megaloureter are bilateral and equally severe on both sides, bilateral splanchnicectomy and sympathectomy done in stages are indicated, with an interval of two or three weeks between operations. If the lesion is less severe on one side, infiltration of the splanchnic nerve on this side may be sufficient, with splanchnicectomy and sympathectomy on the more severely affected side. If this is not sufficient lumbar sympathectomy may also be performed high on the less severely affected side.

Tumors.—Tahara and Hess [11] report two large fatty tumors of the kidney. It is interesting to note that these tumors had existed for a considerable period, that they apparently caused hypertension and loss of weight and that they were both associated with unilateral chronic pyelonephritis. In both cases, nephrectomy reduced blood pressure to within normal limits. Both patients were greatly improved by operation, and both tumors must be considered as benign from the pathologic reports but both had definite malignant characteristics.

Typhoid Infections.—Abramson [12] states that typhoid infection of the kidney is probably commoner than it is believed to be and reports a case of primary renal typhoid infection in a 37 year old white man. Calculi and pyelonephrosis were also present, and enteric typhoid was excluded.

The chain of events leading to primary typhoid disease of the kidney is the ingestion of a massive dose of bacilli followed by transient bacteremia and subsequent renal damage and bacilluria. If renal pathologic changes had occurred previously, the danger of continued infection is greater. The persistence of bacilluria depends on the amount and type of renal damage. In the majority of cases renal typhoid is secondary to enteric typhoid and occurs with the acute infection in convalescence or even years later. With continued renal infection it is usual to find some other pathologic entity of the kidney as a contributing factor. The organism usually is carried to the kidney by means of the blood stream, and bilateral renal infection results. The condition may become unilateral when more serious pathologic changes exist in one kidney and the other kidney clears subsequently.

Renal typhoid may be manifested by bacilluria, pyelonephritis, pyelonephrosis or perinephric abscess. Acute pyelonephritis is characterized by cortical suppurative nephritis and may be associated with pyelitis, ureteritis and cystitis. Pyelonephrosis and perinephric abscesses are usually late manifestations of the same disease process. Miliary abscesses may occur in cases in which the condition is acute, and death

11. Tahara, C., and Hess, E.: Massive Renal Fibrolipoma: Report of Two Cases, J. Urol. **54**:107-115 (Aug.) 1945.

12. Abramson, D. J.: Renal Typhoid Fever: Presentation of a Case of the Primary Type, J. Urol. **54**:422-429 (Nov.) 1945.

occurs. Pyuria alone is associated simply with toxemia. Treatment in general is the same as for other types of bacillary infections of the kidney. Probably one of the most important single factors in treatment is the removal of the obstruction. By the promotion of adequate drainage, infection will be resolved more readily. Sulfonamide drugs, particularly sulfadiazine, deserve further trial. Pelvic lavage with antiseptics or use of an indwelling ureteral catheter is of value.

Hypertension and Hypernephrosis.—Braasch and Goyanna [13] state that nephroptosis per se is seldom, if ever, an etiologic factor in hypertension. In 133 cases of nephroptosis, hypertension was present in 16. In none of these cases was nephroptosis regarded as the etiologic factor. In the majority of cases of nephroptosis the blood pressure is average or less than average. Most of the patients are of the hypotonic type. It would seem that any compression of blood vessels in the renal pedicle which might result from nephroptosis is dissimilar to the pathologic condition in the circulatory system which was involved in the Goldblatt experiment. Urinary retention which may result from nephroptosis does not cause hypertension unless it is accompanied with intrarenal circulatory imbalance, such as sometimes occurs subsequent to secondary urinary infection.

Obstruction.—Soley [14] reviews 19 cases of obstruction at the ureteropelvic junction in children. Ten of the patients were boys and 9 were girls. Their ages were from 8 months to 14 years. Fifteen were 10 years of age or less. The right ureter was involved in 7 cases and the left in 7 cases, and bilateral involvement was present in 5. The factors regarded as causing the obstruction were: stenosis in four ureters, aberrant vessel in seven ureters (2 patients with involvement of the right ureter, 3 with involvement of the left and 1 with bilateral involvement), adhesions in four ureters (2 patients with involvement of the left ureter and 1 with bilateral involvement) and double kidney in 2 cases. In the cases of double kidney the upper ureter overlays the lower, obstructing the latter. The following methods of treatment were employed. Six ureters were dilated, and all the patients were considered definitely improved. Nephrectomy was performed in 5 cases. The results were considered to be failures. All 5 patients were treated late in the course of the disease, and 2 presented palpably enlarged kidneys. Foley Y operation was performed in 3 cases. All patients were considered to have improved. In 1 case the aberrant vessel was severed and nephropexy was performed. Postoperative dilation was performed. The result was good. In 1

13. Braasch, W. F., and Goyanna, R.: Hypertension and Its Relation to Nephroptosis, Tr. Am. A. Genito-Urin. Surgeons **37**:141-144, 1944.

14. Soley, P. J.: Ureteropelvic Obstructions in Children, J. Urol. **55**:46-51 (Jan.) 1946.

case, both ureters were treated only by nephrostomy, use of splinting catheters and severance of adhesions. The result was poor on both sides. In the 2 cases of double kidney, in which the upper ureter blocked the lower, heminephrectomy relieved the lower duct of obstruction and left an important amount of good, functioning tissue. One patient with bilateral involvement refused treatment of any kind.

Pyelocystostomy.—Wright [15] reports a case in which pyelocystostomy was performed, the second operation of its kind so far as he could learn and the first in which only a solitary ectopic, hydronephrotic kidney existed. The patient, a white man aged 42 years, complained of repeated attacks of severe colicky pain in the lower left portion of the abdomen, of five or six months' duration. In the course of the attacks the output of urine was always scanty, and immediately after the attacks, which usually ended suddenly, urine was passed in abundance. Recently he had become conscious of an extremely tender, palpable mass in the lower left portion of the abdomen, which felt to him to be as large as an orange. This diminished in size on the cessation of the attacks of colic but enlarged with the return of the abdominal pains. An intravenous urogram showed that no dye was excreted in one hour from either renal region, and only a faint shadow was seen in the bladder. Cystoscopy revealed that the bladder was normal and both orifices were situated normally. No peristalsis or ejaculations of urine could be seen on either side, and no indigo carmine appeared from either orifice in forty minutes after intravenous injection of the dye. A 5 F. ureteral catheter met an obstruction on the right side, 3 cm. from the orifice, through which the smallest filiform catheter could not pass. On the left side, a 5 F. catheter passed 12 cm. up and tapped urine under strong pressure. Seven fluidounces (210 cc.) of clear urine drained in forty minutes from the catheter in the left ureter. A retrograde pyelogram on the left side revealed an ectopic kidney with a hydronephrotic pelvis. On the right side the ureter apparently ended blindly 3 cm. up from the orifice. At operation the lower border of the renal pelvis was first attached to the lower part of the posterior wall of the bladder by several interrupted sutures of surgical gut, the purpose being to protect the anastomosis to be made from undue tension. An extraperitoneal, suprapubic cystotomy was then made, through which the finger was introduced for guidance. Corresponding vertical incisions, each 3.5 cm. long, were made in the bladder and the renal pelvis, and these were sutured together with surgical gut in the same manner as is employed in gastrojejunostomy. This produced a communication between the cavity of the bladder and the interior of the renal pelvis, through which the index finger could be

15. Wright, B. W.: Pyelo-Cystostomy in a Solitary Ectopic Kidney, J. Urol. **54**:413-421 (Nov.) 1945.

passed easily, without constriction. Five weeks later, cystoscopy showed the stoma to be open and the edges were firmly healed. Eleven months after operation, it was felt that the patient owed his life to pyelocystostomy.

Resection.—Fey [16] distinguishes true partial nephrectomy from the so-called partial nephrectomy, in which one of the two sections of a double kidney with two pedicles and two ureters is removed. In true partial nephrectomy a considerable portion of a single kidney with only one pedicle and one ureter is removed. This involves difficulty in hemostasis and in closure of the corresponding calix. The procedure has been rendered easier and safer by use of the electric knife. In 2 of Fey's cases partial nephrectomy was performed because of renal calculi situated in the lower pole of the kidney. The patients were relieved of symptoms, and the kidney on which operation was performed was functioning at the time of the report. In 1 case partial nephrectomy was carried out because of pyonephrosis involving the lower pole. There was definite improvement after operation, but later total nephrectomy was necessary because a fistula formed in the wound, which had healed previously. Examination of the kidney after removal showed that the origin of the infection was outside the kidney and that the kidney itself was functioning. Therefore, partial nephrectomy had been justified, but this case indicates the need of adequate and prolonged drainage of the perineal space after this operation. In the fourth case partial nephrectomy was done because a clearly defined tuberculous cavity was present and other portions of the kidney were not involved. The patient's condition was greatly improved, but some cystitis persisted, although tubercle bacilli were no longer found in the urine. Nephrectomy was performed, but the patient died four months later as the result of pulmonary abscess. Examination of the kidney after removal showed no active tuberculous lesion; Fey considers that the secondary nephrectomy was not justified in this case.

Ezickson [17] investigated the effect of renal pelvic lavage with a cationic detergent germicide, cetylpyridinium chloride, in a series of 35 cases. The solution was used for one hundred and thirty treatments, and sixty-seven cultures of urine were made and studied. The germicide was used in an aqueous dilution of 1:10,000 or 1:8,000. Of seven classes of organisms involved in infection of the urinary tract, cultures were rendered sterile in 6 cases and no change was observed in 8. When

16. Fey, B.: Quatre observations de néphrectomies partielles, J. d'urol. **52:** 57-61 (May-June) 1944.

17. Ezickson, W. J.: The Effect of Renal Pelvic Lavage with Cetylpyridinium Chloride upon Urinary Tract Infection and Urolithiasis, J. Urol. **54:**235-240 (Sept.) 1945.

previous cultures of urine were negative, all subsequent cultures were negative after renal lavage, demonstrating the ability of this germicide to prevent infection. There was no evident alteration in the clinical course of the urolithiasis.

The germicide was used routinely in 260 cases for renal pelvic lavage, ureteral catheterization, cystoscopy, irrigation of the bladder or instillation in the bladder and urethral dilatation or instillation. In no instance were signs or symptoms attributable to infection due to instrumentation. On the other hand, in some of the cases, infection of the bladder and urethra disappeared after its use. In no case was there any evidence of irritation attributable to the germicide. It would seem from this study that cetylpyridinium chloride in a concentration of 1:10,000 or 1:8,000 can be used routinely as an effective germicide for instillation into the urinary tract prior to or accompanying instrumentation. It has also proved effective in the treatment of certain infections of both the upper and the lower parts of the urinary tract.

URETER

Stone.—When a calculus is situated in the lower part of the ureter within 2 to 6 cm. of the ureteral meatus and is palpable on vaginal examination, Leger and Germain [18] maintain that it is best removed by the vaginal route. This operation has not been used frequently in France, but many cases in which this method was used, with good results, have been reported in the American literature. The authors report 1 case in which this method was employed. Dissection of the ureter is performed behind and to the side of the calculus; when the ureter is freed sufficiently it is brought out through the incision in the vaginal wall, and the stone is removed through an incision in the ureter. After removal of the stone the ureter is sutured with fine surgical gut. While some surgeons have used an indwelling ureteral catheter for twenty-four hours after this operation, others do not consider this necessary. The authors did not use a catheter in the case reported, merely a small drain in the vaginal incision before suturing. The drain was removed in forty-eight hours. No postoperative complications occurred.

Prince [19] states that Foley's lumbar ureterolithotomy should be performed immediately in all cases of calculus in the upper third of the ureter, unless they are of such small size that they give great promise of spontaneous passage within a brief period. This operation is carried out through an incision from 7 to 8 cm. in length without cutting any

18. Leger, L., and Germain, A.: L'uretérolithotomie par voie vaginale, J. d'urol. **52**:1-4 (Jan.-Feb.) 1944.

19. Prince, C. L.: Lumbar Ureterolithotomy: The Foley Operation, J. Urol. **54**:368-373 (Oct.) 1945.

muscle; the ureter is never freed from its bed, and there is a minimum of retroperitoneal dissection. The operation is of beautiful anatomic design and is quick, bloodless and effective. The average postoperative stay in the hospital has been seven days, as compared with 18.4 days in a series of similar cases in which operation was performed by the usual methods of lumbar ureterolithotomy, both muscle cutting and muscle splitting. The postoperative course is extremely smooth, and morbidity is reduced to a minimum.

Dourmashkin [20] discusses cystoscopic treatment of stones in the ureter in his series of 1,550 cases of stones situated at all levels of the ureter and renal pelvis. Cystoscopic manipulation was carried out in 1,253 cases, and in 1,171 cases (93.5 per cent) the stone was expelled. There were no instances of ruptured ureter or mortality resulting from instrumentation. To form a true index of what may be accomplished by transurethral methods, the cases were divided into two groups: (*a*) patients having small stones, less than 5 mm. in width (689 cases), and (*b*) those having large stones, 5 mm. and more in width (564 cases). In group *a*, the stone was passed in 99.7 per cent of cases and in group *b* in 85.9 per cent.

The principle of providing ample room for the downward passage of the stone at and below its level was followed in this work. This was achieved by dilation of the lower end of the ureter with metallic bougies and by using rubber bags at the higher levels. Passage of an ordinary catheter was sufficient to induce the expulsion of a small stone in the majority of cases. A number of mechanical factors maintain renal drainage in cases of ureteral stone. For this reason patients were allowed to go about with the stone for considerable lengths of time, without any appreciable renal injury. The majority of patients were ambulatory in the period in which treatment was being given. Indwelling multiple catheters do not provide adequate dilatation in cases of large stones and are likely to produce renal infection.

Forcible extraction of stones in Dourmashkin's opinion is contraindicated, as the same results may be obtained by more conservative methods outlined in the work, without subjecting the ureter to the ever present likelihood of grave injury.

Sauer [21] reports a case of ureterocele complicated by formation of stones within the wall of the cyst, extension of the formation of stones into the juxtavesical part of the diseased ureter and additional calcareous deposits on the outer wall of the ureterocele. In spite of the extensive-

20. Dourmashkin, R. L.: Cystoscopic Treatment of Stones in the Ureter with Special Reference to Large Calculi, Based on the Study of 1,550 Cases, J. Urol. **54**:245-283 (Sept.) 1945.

21. Sauer, H. R.: Case of Ureterocele with Stone Formation in Ureter, Ureterocele and Bladder, J. Urol. **54**:158-161 (Aug.) 1945.

ness of the lesions no significant changes had developed in the upper part of the urinary tract. Administration of the stone-dissolving agent solution G by means of continuous drip irrigation of the bladder resulted in complete disappearance of the incrustations. Thus the wall of the cyst was rendered suitable for transurethral coagulation, and delivery of the stones from the ureterocele and ureter was possible.

When a stone in the lower end of the ureter is not visualized by roentgenologic means, Chevassu [22] found that retrograde ureteropyelography can be carried out. Although the ureteral sound cannot be introduced past the obstruction, the opaque medium introduced into the meatus will pass the obstruction. In the case reported, this procedure was carried out on two different occasions, at an interval of four years. The right side was involved in the first attack and the left side in the second attack.

In both instances the lower portion of the ureter was contracted and the ureter was dilated above the contraction. Chevassu attributes the contraction to spasm caused by the presence of the stone. On the first occasion a small stone was passed spontaneously, with complete relief of symptoms. On the second occasion the stone passed after dilation of the ureter. The best method of localization of a calculus in the lower end of the ureter is by rectal palpation in men and vaginal palpation in women. In women who are thin bimanual examination may be employed, and the calculus may be palpated between the fingers of the hand on the abdomen and the finger within the vagina. In some cases it may be possible to manipulate the stone out of the ureter by this procedure.

Carcinoma.—Lazarus and Marks [23] review the literature on primary carcinoma of the ureter and report a case. In 1934, Lazarus collected 68 cases, including 3 of his own. Since then 115 additional cases have been reported. This increased number of cases indicates greater alertness on the part of urologists to the possibility of this disease rather than to an actual increase in incidence. Of the total number of tumors, 42 per cent were of the nonpapillary type. Malignant neoplasms of the ureter were situated in the lower segment of the ureter in approximately 50 per cent of the reported cases and were associated with extasia of the renal pelvis in 46.4 per cent and of the ureter in 43.7 per cent, due to a tendency for these tumors to occlude the lumen of the ureter. The greatest prevalence of this disease occurred in the sixth and seventh decades. Ureteral carcinomas have pronounced invasive and metastasizing tendencies, par-

22. Chevassu, M.: Les calculs de l'extrémité inférieure de l'uretère invisibles aux rayons X, J. d'urol. **52**:39-41 (March-April) 1944.

23. Lazarus, J. A., and Marks, M. S.: Primary Carcinoma of Ureter, with Special Reference to Hydronephrosis, J. Urol. **54**:140-157 (Aug.) 1945.

ticularly to the regional lymph nodes (28.9 per cent), liver (14.9 per cent) and bones (12.8 per cent).

Although pain, hematuria and the presence of an enlarged kidney are supposed to constitute the characteristic triad of symptoms of this disease, Lazarus found that hematuria alone was by far the outstanding symptom, having occurred in 70.5 per cent of the collected cases. The diagnosis of ureteral tumor cannot be made from symptoms or physical signs, but it can be made from carefully executed and correctly interpreted cystoscopic and roentgenologic findings. Although the presence of a tumor at a ureteral meatus is an extremely suggestive finding, it was noted in only 25.1 per cent of cases reviewed in this series. A clearcut and persistent filling defect, visible in the ureterogram, especially when associated with ectasia of the segment of ureter directly above such a defect, constitutes the only pathognomonic sign of ureteral tumor. Unfortunately, however, because of technical difficulties or of failure to obtain carefully made ureterograms, such defects were demonstrated in only 21.8 per cent of the collected cases.

The chances of demonstrating filling defects in ureterograms would be enhanced if repeated attempts were made to obtain good ureterograms in all cases in which (1) an obstruction is present in the ureter, (2) bleeding occurs through the ureteral catheter as a result of manipulation at the site of the obstruction and (3) no calculus is found at the site of obstruction. Failure to recognize the presence of this disease has led urologists to remove hydronephrotic kidneys only to learn later that hematuria had recurred, thereby necessitating a second operation, for removal of the tumor-bearing segment of ureter. Owing to the difficulty at times of palpating a tumor within the ureter at exploration of the upper part of the urinary tract for hematuria, it seems a better policy to remove the entire ureter along with the kidney, especially when the cause for the bleeding is not found in the kidney. This is particularly true in cases of hydronephrosis or pyonephrosis in which the cause of the pelvic ectasia is not clearly discernible. The procedure of choice in the treatment of this disease is complete extraperitoneal nephroureterectomy. It is recommended that a cuff of vesical wall surrounding the ureteral meatus be included in the operative procedure in cases in which the tumor is situated low down in the ureter, especially when the ureteral meatus is involved.

A careful review of the literature showed the dangers of incomplete urologic examinations for so-called minor urologic complaints. This is clearly demonstrated in the history presented in 1 of the cases reported by Lazarus and Marks, in which the patient was treated perfunctorily for fifteen years for cystitis without being subjected to a thorough urologic examination. The authors feel certain that this lesion would

never have progressed to such large proportions had ureteral catheters been passed during one of the episodes of so-called cystitis.

Bowie and Bors [24] report a case of primary papillary carcinoma of the ureter complicated by severe infection, which made diagnosis more difficult. The operative technic is reported in detail because in this particular case certain well recognized general surgical principles of attacking malignant tumors were employed. The peritoneal cavity was opened to search for evidence of spread of tumor. Dissection was begun in healthy tissue above the tumor, and, after the tumor was reached from above, dissection with an electrosurgical knife was begun on the side of the bladder and the whole tumor removed en masse.

Ureteral Transplantation.—Davalos [25] reports a new technic of transplanting both ureters to the rectosigmoid at one operation, together with a report of its experimental employment in 10 dogs. In this operation the ureters are transplanted to the anterior aspect of the rectosigmoid, in the median line (the areas covered by mesenteric circulation being avoided), and a 4 cm. transverse incision in the bowel is utilized. The method differs fundamentally from all previously reported technics.

The operation has the following advantages: 1. The main blood supply of the intestine comes from the mesentery and transversely surrounds the intestine; therefore, a transverse cut in the intestine causes much less damage to the blood supply than does a longitudinal incision, and the bleeding is minimal. 2. Only one operation is required to transplant both ureters in the same incision; consequently the operative work, trauma and chances of leakage are reduced 50 per cent. 3. With this transverse incision it is possible to form a large mucosal flap which acts as a valve and protects the anastomosis against retrograde infection. This flap is formed by the action of the mattress sutures, which, when tied, shorten the intestine on its transverse aspect. 4. The drainage of the ureters is under direct observation of the surgeon during the entire procedure. If the ureters are draining satisfactorily before the mattress sutures are tied, there is no danger of their compression after the sutures are tied.

It is concluded from this study that this new method of transplanting both ureters at the same time is safe and effective. The results in animals have been excellent. In no instance did hydronephrosis follow these experimental operations, one of which was performed one year before the report.

---

24. Bowie, C. F., and Bors, E.: Primary Carcinoma of the Ureter, J. Urol. **54**:434-437 (Nov.) 1945.

25. Davalos, A.: New Technique of Simultaneous Bilateral Uretero-Intestinal Anastomosis: Report of Experimental Study, J. Urol. **54**:357-367 (Oct.) 1945.

PROSTATE

Transurethral Operation.—Greene and Thompson [26] state that introduction of the transurethral method of prostatic operation has removed one of the chief contraindications to prostatic surgical treatment, namely, advanced renal insufficiency. Transurethral prostatic resection can be performed safely on patients suffering from advanced renal insufficiency, and these patients are no longer obliged to lead a life with an indwelling catheter. The important features of management are: (*a*) improvement or restoration of the acid-base metabolism by the intravenous administration of suitable fluids and the treatment of anemia by blood transfusions; (*b*) maintenance of a urinary output of 2,000 to 3,000 cc. daily, thereby producing a fall in the nitrogenous waste products present in the blood; (*c*) drainage by urethral catheter for as short a period as possible (suprapubic cystotomy, with its attendant mortality rate, is not necessary); (*d*) operation at the first indication that the value for blood urea is no longer falling but has become stabilized, and (*e*) completion of the resection in forty-five minutes. The period of preoperative and postoperative hospitalization for patients suffering from advanced renal insufficiency is comparatively short when they are treated by transurethral prostatic resection. Longevity following prostatic resection among patients of this group warrants the procedure. Gastrointestinal symptoms due to renal insufficiency have all been relieved in spite of the fact that renal function remains impaired.

Emmett and his associates [27] state that more than 94 per cent of transurethral prostatic operations performed at the Mayo Clinic were completed in one stage. More than 3.8 per cent of the patients were 80 years of age or older, and the average age for the entire group was 66 years. The average postoperative hospitalization was eight and a half days. Only 7.6 per cent of patients were confined to the hospital for two weeks or more after operation, while only 2.1 per cent were confined for three weeks or more. Eighty-two per cent of the patients were operated on without preliminary drainage. The remaining 18 per cent were prepared by urethral catheterization except for 7 patients (less than 1 per cent) who had suprapubic drainage before resection. The operative mortality rate was 1.3 per cent. In the past few years interest has been increased in transurethral resection of the vesical neck for urinary retention caused by injuries or diseases of the spinal cord. Interest in this subject has increased greatly throughout the country because of the large number of injuries to the spinal cord received in combat by members of the armed forces.

---

26. Greene, L. F., and Thompson, G. J.; Transurethral Prostatic Resection in Patients with Advanced Renal Insufficiency J. Urol. **54**:166-173 (Aug.) 1945.

27. Emmett, J. L.; Cook, E. N.; Pool, T. L., and Greene, L. F.: Transurethral Surgery in 1944, Proc. Staff Meet., Mayo Clin. **20**:469-472 (Nov. 28) 1945.

One hundred and seventy-one patients who had carcinoma of the prostate gland underwent transurethral resection at the Mayo Clinic in 1944. Bilateral orchectomy was performed in 17 of these cases and in 4 other cases in which no prostatic operation was performed. In 1944, bilateral orchectomy was advised only when metastasis was present and giving rise to symptoms.

One of the most important procedures in transurethral operation is transurethral manipulation of ureteral calculi. In the order of frequency with which they are used, the Johnson, Councill and Howard spiral extractors are the three stone extractors employed in this work. Only stones in the lower third of the ureter are considered suitable for manipulation. Manipulation of ureteral calculi is an exceedingly difficult technical procedure and should be so considered if a high percentage of successful results is to be obtained and if serious trauma of the ureter is to be avoided. The most important rule is that the manipulation must be done with extreme gentleness. A catheter or extractor should never be forced past the stone. If the instrument cannot be passed with gentle manipulation, some other means should be resorted to for removal of the calculus. Forceful manipulation may result in perforation of the ureter, and after this is done it is usually extremely difficult or impossible to pass a catheter up the ureter for drainage. It is apparent, then, that sufficient room in the ureter in the region of the stone is necessary for successful manipulation. At times a 4 or 5 F. catheter can be passed beyond the stone, yet there is insufficient room for an extractor to pass. In such a case, if the catheter is left in place for from twenty-four to forty-eight hours, enough dilatation may be obtained for passage of the extractor. If the stone is impacted in the intramural portion of the ureter, the roof of the ureter may be excised with a Collings knife through a McCarthy panendoscope, the indwelling ureteral catheter being used as a guide. In this manner the stone may be exposed and flipped into the bladder, or the extractor may then be passed to engage the calculus. When one resorts to such a procedure, it is always wise to have a catheter in the ureter as a guide as after the first cut with the Collings knife it may be difficult to discern the true channel of the ureter.

One of the most disturbing complications that may harass the surgeon in transurethral manipulation of a stone is that he may engage a large stone in the extractor but be unable to pull it through the intramural portion of the ureter or ureteral meatus. One simple satisfactory maneuver may be used in this situation. The cystoscope is removed and the extractor left in place, with the stem of the extractor passing out through the urethra. An 18 F. catheter is passed alongside the stem of the extractor into the bladder and left in for drainage.

The extractor is left in place for from twenty-four to forty-eight hours. At the end of this time the patient is returned to the operating room and is anesthetized. The catheter is removed, and the cystoscope is introduced into the bladder. The stem of the extractor is threaded through the cystoscope. It is usually rather simple at this stage to extract the stone, as the wire basket on the extractor has produced considerable dilatation and only a moderate amount of traction is necessary to complete the procedure.

Emmett and his colleagues are convinced that suprapubic cystotomy for the removal of vesical calculi is only rarely necessary. It is unusual to encounter a stone so large that it cannot be crushed with the Bigelow type of lithotrite. In 1944, litholapaxy was carried out successfully in 56 cases at the clinic. Only 2 patients underwent suprapubic removal of stones. In almost all the cases litholapaxy and transurethral resection were carried out as a one stage procedure. Usually litholapaxy is done first. In an occasional case, however, intravesical tissue may make litholapaxy impossible, so that at least part of the prostatic resection must be done first. Most patients experience no more postoperative reaction from combined litholapaxy and transurethral resection than from transurethral resection alone.

Carcinoma.—Darget [28] reports treatment of carcinoma of the prostate with radium, using different methods of application. In 1 case in which prostatectomy had been performed previously, a urethral sound containing two tubes of 10 mg. of radium each was left in situ for three days; the patient was in good health three years later. In 2 cases treatment consisted in implantation of radium needles by both the transvesical and the perineal route. One of the patients was living and well seven years after treatment and the other two years after treatment. In 2 cases, transurethral resection was combined with implantation of radium needles by the perineal route. Both of these patients were living, without signs of recurrence, two years after treatment. Two other patients were treated by perineal implantation of radium alone; these patients were both living and well, 1 nearly six years and the other nearly four years after treatment.

Darget considers that in the initial stage of carcinoma of the prostate the best results are obtained by the implantation of radium by the transvesical and the perineal route simultaneously. If considerable residual urine is present, transurethral resection combined with implantation of radium by the perineal route is indicated, provided that the tumor is not too large. If no residual urine is present and the tumor is relatively small, perineal implantation of radium alone is indi-

28. Darget, R.: Le traitement actuel du cancer prostatique, J. d'urol. **52:** 29-32 (March-April) 1944.

cated. In cases in which infection is present or in those in which there is danger of uremia, preliminary cystostomy is indicated and it should be followed by transurethral resection and radium therapy. In cases in which cure appears impossible and the growth is in an advanced stage, transurethral resection relieves the urinary obstruction and is the best palliative measure. For both transvesical and perineal implantation, needles of 3 mg. of radium each are employed; by the transvesical route, these needles are placed 15 mm. apart and by the perineal route 1 cm. apart. For perineal implantation, four to eight needles are used, depending on the size of the tumor. Cystostomy is necessary before transvesical implantation. For perineal implantation alone, an indwelling catheter is employed during the time that the radium implants are in place and for several days thereafter. It has been found that treatment with radium by the perineal route is well tolerated.

In discussing the paper by Nesbit and his associates, Dean [29] states that they established a group treated by castration and, as nearly as possible, a comparative group treated with 1 mg. of diethyl stilbestrol daily. The immediate effects of castration appear to be more spectacular than those of diethyl stilbestrol in the doses mentioned. Whereas the pain from metastasis to bone often disappears within twenty-four to forty-eight hours after operation, relief with the drug frequently is noted only after a week or more.

Dean observed a greater softening and shrinking of the primary tumor after administration of diethyl stilbestrol than after castration. Sixty per cent of Dean's patients relapsed in seven to eight months. He found little difference in the duration of improvement before relapse occurred, whether treatment was with diethyl stilbestrol or castration. The patients who received diethyl stilbestrol and did not relapse at the usual time survived longer and with less evidence of persistence of the primary tumor than did those who underwent orchectomy. After relapse occurs, irrespective of the type of treatment first given, Dean has found little benefit in further treatment. The castrating of patients treated with diethylstilbestrol has not helped, and the treatment of castrated patients with the drug has been equally unavailing. Nor has there been any noteworthy quantitative improvement after the dose of diethylstilbestrol has been increased. In general, patients have improved in proportion to the degree of feminization they show. The men with shrunken external genitalia, enlarged breasts with pigmented nipples and areolas and added weight about the hips have shown greater regression in prostatic carcinoma than have the patients in whom these changes were less pronounced or absent. Dean questions the ability of the most

29. Dean, A. L., in discussion on papers of Huggins and McDonald, Rathbun and Nesbit and others, Tr. Am. A. Genito-Urin. Surgons **37**:232-235, 1944.

experienced urologist to be correct invariably if examination is limited to rectal palpation. None of his patients were treated unless the diagnosis was verified microscopically. Dean makes aspiration biopsies, which he has accepted as being accurate because of the extraordinary experience of the pathologist with whom he works. It is a rare prostatic carcinoma which can be positively recognized by rectal touch before it becomes inoperable. Then even the most radical operation cannot be carried out.

BLADDER

Carcinoma.—Graves and Thomson,[30] in discussing total cystectomy for carcinoma, state that this operation should be performed with the intent to cure and under conditions which render cure possible. It should not be selected, in their opinion, as a method of palliation when the tumor has obviously spread beyond the limits of the vesical wall. They have performed this operation in 28 cases and state the belief that cystectomy is a sound and highly valuable procedure and that in the future it will be employed oftener and with increasingly satisfactory results. The first of the 28 patients was operated on in September 1933. Thirteen of the group are living and free from malignant disease as determined at the time of the last report. The length of the time of survival after cystectomy varied from one month to ten and a half years. Of the last 20 patients, encountered after 1939, 11 patients were living and had no apparent evidence of recurrent carcinoma at the time of their report.

The indications for cystectomy have become definite and clearcut. First, there should be reasonable assurance, based on every possible form of investigation, including abdominal exploration, that no distant metastases are present and that removal of the bladder and its adjacent structures will remove the tumor of the bladder completely. Further, it must be decided that age and general condition will permit the patient to survive the operation and live to enjoy its benefits. As far as age is concerned, Graves and Thomson have adopted a tentative upper limit of 60 years for this procedure and in older patients have hesitated to advise cystectomy. The choice of cystectomy as far as the disease within the bladder is concerned depends on the extent and manner of growth and location of the tumor more than on the result of biopsy. Multiple tumors, often of low grade malignancy, call for cystectomy when they involve so much of the vesical mucosa that local resection is impracticable and destruction by electrocoagulation and radium will virtually destroy the bladder itself. High voltage roentgen therapy should not be relied on in most instances as a method of cure. Its use may be attended by actual disadvantage, moreover, when operation becomes necessary later. This

30. Graves, R. C., and Thomson, R. S.: Total Cystectomy for Carcinoma, Tr. Am. A. Genito-Urin. Surgeons **37**:73-82, 1944.

is particularly true of ureterointestinal anastomosis which may be affected adversely by roentgen therapy, probably through the fibrosis which it produces in the walls of the bowel and ureter.

Extensive infiltrating carcinoma, still confined to the bladder, also presents an indication for cystectomy, since radium and roentgen rays usually do not cure tumors of this type and local excision is equally ineffective in most cases. Tumors of the outlet of the bladder, particularly those which overlie the prostate in men, give still another reason for cystectomy, because electrocoagulation and irradiation sufficient to destroy the growth in this region will seriously impair the usefulness of the bladder through occlusion of the urethra and destruction of sphincteric function. Tumors of the bladder contiguous to the prostate are not controlled by radium or any other method of treatment short of complete surgical extirpation of the structures involved.

Finally, tumors of the trigone demand cystectomy when they occlude both ureters or when they encroach on the ureters so closely that their ultimate occlusion, as a result of disease or local treatment, is inevitable. The successful end results of operation for malignant disease of the bladder will depend on the preservation of adequate renal function as well as on the cure of the lesion. Pronounced occlusion of the ureters, one or both, should be regarded to be of serious prognostic significance, since periureteral invasion leads readily to the invasion of lymphatics beyond the limits of the bladder itself.

The final evaluation with reference to the choice of treatment is made at the time of cystoscopic and rectal examinations with the patients under spinal anesthesia. The authors regard this routine use of anesthesia as the most helpful preoperative step that they have taken in the study of these patients. The patient is relaxed and comfortable; the surgeon is not hurried, and the filling and emptying bladder may be watched at leisure. The nature, location and extent of the tumor may be determined better in these circumstances than in any other way. More of the bladder is brought into view, and the relations of the neoplasm to the ureteral orifices and the vesical outlet are much more accurately defined. Most important information with reference to the possibility of cystectomy is obtained finally by rectal examination with the patient under anesthesia. One learns in this way the true size of the tumor if it is palpable, the degree of infiltration through the wall of the bladder, the movability of the mass and its distance of separation from the rectum and the lateral wall of the pelvis.

Graves and Thomson use spinal anesthesia induced by the continuous method of administration, and they have found this technic to be invaluable in these cases. The necessity for a large amount of anesthetic given in one initial dose is avoided; the hazards of shock are greatly

lessened, and patients emerge from prolonged procedures in highly satisfactory condition. The authors also give a description of their method of cystectomy.

Smith,[31] in discussing Graves's article, states the belief that total cystectomy is going to be performed more and more frequently. Smith expresses the opinion that total cystectomy is not a particularly dangerous procedure, as he has performed cystectomy in 10 cases of carcinoma, with only one death. One woman died of coronary disease (proved at necropsy) ten days after the second operation. Her case was unusually successful from the point of view of the operation, as there were no metastases and both kidneys were functioning well.

Jewett [32] gives an analysis of 107 cases of infiltrating carcinoma of the bladder in which necropsy was performed at the Johns Hopkins Hospital. Four important facts were revealed: First, the potential curability varies inversely with the degree of penetration of the wall of the bladder. Second, while the tumor is still confined to the submucosa or muscularis a latent period exists, in which the potential curability is relatively high. Third, complete penetration of the muscularis is associated with low potential curability. Fourth, complete penetration usually causes stony hard induration. This induration in more than 80 per cent of the cases can be recognized by rectoabdominal palpation with the patient under anesthesia, but when doubt exists the induration can be detected readily at laparotomy, at which time the regional lymph nodes and liver also can be examined.

Deming and Lindskog [33] report a case of papillomatosis of the bladder and the urethra. Involvement of the whole urethra by metastases, late metastasis to the right lung and successful surgical treatment of both, the former by excision of the penile urethra and the latter by a pneumonectomy, make the report unique. Although the primary lesion had been fully under control for thirteen years metastasis to the right ilium had developed at the time of this report, and other osseous metastases will probably develop. The histologic classification of papillomas of the bladder gives no opportunity for optimism toward its inherent metastatic quality. The justification of eradication of a solitary distant metastatic lesion is supported on the basis of relief of symptoms and prolongation of life.

---

31. Smith, G. G., in discussion on papers of Deming and Lindskog,[33] Jewett,[32] Scholl and Graves and Thomson,[30] Tr. Am. A. Genito-Urin. Surgeons **37**:83-84, 1944.

32. Jewett, H. J.: Infiltrating Carcinoma of the Bladder, Tr. Am. A. Genito-Urin. Surgeons **37**:51-65, 1944.

33. Deming, C. L., and Lindskog, G. E.: Papillomatosis of Bladder and Entire Urethra; Infiltrating Cancer of Bladder; Late Pulmonary Metastasis; Successful Pneumonectomy, Tr. Am. A. Genito-Urin. Surgeons **37**:39-50, 1944.

Reflux.—In tuberculosis of the urinary tract involving the bladder, reflux of urine from the infected bladder may occur. Bouchard [34] states that the reflux is due to the destruction of the normal mechanism of the ureteral meatus by the tuberculous lesion in combination with excessive urination and tenesmus of the bladder, which occur in tuberculosis of the urinary tract. Another important factor is the involvement of the vesical neck; inflammatory lesions, even superficial, of the mucosa cause spasmodic contracture of the sphincter. This is not the only cause for failure of normal function of the vesical neck and sphincter. Inflammatory lesions may involve the musculature and especially the interstitial connective tissue, resulting in fibrosis. In renal tuberculosis, the reflux of urine not only affects the infected kidney, but also endangers the opposite kidney. After removal of the affected kidney, if the cystitis persists, reflux of urine may involve the remaining kidney or it may create a fistula in the lumbar wound with discharge of urine through the fistula.

Bouchard reports 5 cases in which such a fistula occurred in the lumbar wound after removal of a tuberculous kidney. He reports 3 cases in which cystography showed reflux to the uninvolved kidney in cases of unilateral renal tuberculosis and 3 cases in which reflux to the remaining kidney occurred after nephrectomy. In cases in which the cystitis cannot be cured by the use of an indwelling catheter and irrigations with antiseptic solutions, especially methylthionine chloride, Bouchard recommends endoscopic resection of the vesical neck, which he considers the best surgical treatment for the relief of urinary reflux.

Traumatic Paralysis.—Campbell [35] states that 1 in approximately 30 infants is stillborn and that in about 30 per cent death results from trauma at birth. In 11 to 35 per cent of the group in which death results from trauma, the central nervous system is injured, chiefly by tentorial tears, compression, contusion, crushing or laceration of the brain or spinal cord or of both. Hemorrhage into or about these structures is the striking observation at necropsy. Literature on obstetrics offers no data regarding the incidence of birth trauma as it affects urinary control; yet, by analogy, since injury of the central nervous system in adults commonly produces pronounced disturbances of vesical function, so it must in the newborn. These disturbances usually pass unrecognized at the time but, if the infant survives, may present serious clinical problems in succeeding months. Attention has been called to the late effect of birth paralysis, but apparently it has not been suggested that when

34. Bouchard, R.: Le reflux dans la tuberculose rénale, J. d'urol. **51**:133-146 (Nov.-Dec.) 1943.

35. Campbell, M. F.: Traumatic Cord Bladder in a Premature Infant: Successful Treatment by Indwelling Catheterization, Tr. Am. A. Genito-Urin. Surgeons **37**:17-19, 1944.

infants have traumatic neurovesical disease the same fundamentals of urologic treatment be observed that apply when the patient is an adult.

Campbell reports a case of injury of the central nervous system at birth which was complicated by traumatic spinal cord bladder in a prematurely newly born infant. The patient was a girl who had been born one month prematurely. A few hours after birth she became cyanotic, yet cried vigorously. Later the child was listless, respirations were shallow and irregular, icterus, grade 1 plus, was noted and subconjunctival hemorrhages in the left eye were observed. A soft doughy mass extending from the pubic region to the umbilicus was detected but disappeared on catheterization. Catheterization and dilation of the urethra to 12 or 15 F. was also recommended, since at that time Campbell thought that retention was probably due to a congenitally tight urethra. It was not until the next day that the neurologic nature of retention was demonstrated. On this day the condition was decidedly worse, respirations were shallow, with an occasional gasp, and dark red blood clots were present in the pharynx. The persistent distention of the bladder was relieved by drainage by an indwelling catheter, which remained in place for one week. Scattered leukocytes were found in the urine, and on culture a mixed infection of colon bacillus and Staphylococcus aureus was found. The day after the institution of indwelling catherization it was noted that the child was definitely improved, respirations were regular and she opened her eyes and responded to stimuli. Relief of pressure of the spinal fluid by spinal tap may also have been a beneficial factor. It was believed by all who saw this patient that the employment of the indwelling catheter at the critical period of vesical retention saved her life.

VARICOCELE

Campbell [36] stated that practically all varicoceles in young boys may be classified etiologically as symptomatic, that is, they result from interference with the spermatic venous return, usually by extravascular compression. The last is often the late result of renal trauma and the extensive changes in the perirenal tissue which so commonly follow. The discovery of varicocele in a prepuberal male calls for thorough urologic examination and removal of the etiologic mechanical factor rather than for varicocelectomy. In 1 of Campbell's cases, the patient was a boy 13 months old. A large varicocele on the left side promptly disappeared after nephrectomy for Wilms's tumor. In this instance the tumor was recognized before the varicocele. In contrast, in another case, that of a boy 13 years old who was referred for varicocelectomy, investi-

36. Campbell, M. F.: Varicocele Due to Anomalous Renal Vessel: An Instance in a Thirteen-Year-Old Boy, Tr. Am. A. Genito-Urin. Surgeons **37**:13-14, 1944.

gation prompted by the presence of the varicocele revealed asymptomatic hydronephrosis secondary to ureteral compression by an aberrant lower polar renal artery. This artery also compressed the upper part of the left spermatic vein. Treatment in the last-mentioned case consisted in division of the obstructing renal artery and, doubtless unnecessary, similar division of the spermatic vein at the upper end of the large retroperitoneal varicocele. The swelling in this case extended from the testicle to the point of compression of the spermatic vein by the anomalous renal vessel. Three months after operation scrotal palpation disclosed no varicocele, but hydronephrosis due to periureteral scarring existed three years later.

URINARY CALCULI

In one year of urologic investigation and practice in a hospital that supplies medical care to the southern part of Ecuador, in 60,000 patients Davalos [37] did not find a single stone in the urinary tract. In the wet tropics the high temperature induces profuse perspiration which, by eliminating a considerable part of the metabolic output through the skin, materially decreases the strain on the kidneys. The low urinary p_H prevents the growth of urea-splitting organisms (Proteus vulgaris, Proteus ammoniae, Escherichia coli and others), and phosphates and carbonates do not precipitate in the urinary tract. It would appear that, in tropical Ecuador at least, climatic conditions are primarily responsible for the rarity of urinary lithiasis, since the poorly balanced vitamin-deficient diet of the inhabitants far from preventing the formation of stones is conducive to it.

Vermooten [38] states that renal calculi are rare in South African Negroes. He checked 1,000,000 cases of Negroes to a hospital and found only 1 Negro who had renal calculi. The climatic conditions in South Africa are different from those of Ecuador. Although the coastal belt is hot and moist, the climate as a whole is dry and of the desert type, with hot days, cold nights and a short rainy season.

As Davalos has pointed out, in certain areas in the United States calculi are common and in others they are relatively rare. This indicates that other factors are also at work, especially when such episodes as the "stone wave" which swept over Europe, especially Germany, after the first World War are considered. His observations on dietary habits and the acidity of the urine are especially important. He expressed the opinion that these played a considerable part in the absence of calculi in South African Negroes for their diet also tends to have an acid-ash base. The water supply as well as the diet may be of great significance. The diet of the South African Negroes is poor in calcium. Their normal

37. Davalos, A.: The Rarity of Stones in the Urinary Tract in the Wet Tropics, J. Urol. **54**:182-184 (Aug.) 1945.

38. Vermooten, V., in discussion on Davalos,[37] p. 185.

daily intake of calcium is much less than that which most textbooks on dietetics indicate to be the normal daily minimal requirement; yet they have a magnificent bony structure and excellent teeth, with few caries. Renal calculi are found in American Negroes though to a less extent than in the white persons. This brings up the point that some racial characteristic may be present. This was emphasized in the observations in South Africa, in which it was found that "Cape-colored" persons (half caste race of mixed Negro and Caucasian blood) had almost as many calculi as Caucasians.

Keyser [39] discusses some of the evidences of the origin of urinary calculi from the physicochemical, bacteriologic and pathologic standpoints as revealed by experimentation on animals and study of stone-forming kidneys. He presented the concept of stone-forming pyelonephritis, which parallels in some degree that of other types of crystalline deposition in tissue. Stone dissolution was discussed from the standpoint of the chemist and of the clinician. It has been and will be further developed.

MULTIPLE TUMORS

Hayward [40] reports a case of four primary malignant tumors in a man who was 82 years of age at the time of the report. In order of appearance in a period of two years, they were: (1) basal cell carcinoma, (2) epidermoid carcinoma, (3) adenocarcinoma of the prostate and (4) embryonal carcinoma of a testis. Hayward comments briefly on the literature. He states that Warren and Gates were able to find only 3 cases of three or more primary malignant lesions. Bugher reported 3 cases of three primary malignant lesions. From these reports it must be recognized that the presence of three or four primary malignant lesions is extremely rare and makes this case worthy of reporting. Another unusual feature of the case is the occurrence of an embryonal carcinoma of the testis in a patient of advanced age.

Lombard and Warren, in a recent publication, offer the following conclusions: "There is a greater susceptibility to cancer in persons having one cancer than in the normal population. Whether this susceptibility is caused by the first cancer or is inherent in the individual is not known. There is no evidence to assume that the presence of a skin cancer inhibits other cancers. If anything, the evidence points to the contrary."

---

39. Keyser, L. D.: Studies in Urinary Calculosis, J. Urol. **54**:194-210 (Aug.) 1945.

40. Hayward, W. G.: Multiple Primary Tumors, J. Urol. **54**:307-311 (Sept.) 1945.

SCHISTOSOMIASIS

The recognition by Peters, Huntress and Porter [41] of 2 cases of bilharziasis, the first in Maine to be added to the literature, increases to 37 the reported proved cases in the United States and Canada and brings this condition to the attention of the urologist at an opportune time. Geographically the distribution of the disease is governed by the existence of a suitable snail host necessary for each of the three types of schistosomes which infect the human body. The finding of the ova in the urine or at biopsy is necessary for a positive diagnosis, but suspicion of the existence of the condition from the history of the case, the symptomatology and the blood picture is grounds for specific treatment.

Man is usually infected by the schistosomes in the water when his skin becomes penetrated by the free-swimming cercariae, whose larvae subsequently migrate into the blood vessels. They are carried to the heart and capillaries of the lungs and are said to reach the liver and remain in the portal system, where they develop and mature. The time required for their ovulation varies with the different species from twenty-seven to sixty days. The site of egg laying depends on the habits of the particular species of worm. Schistosoma haematobium deposits its ova particularly in the vesical wall, and Schistosoma mansoni and Schistosoma japonicum usually in the venules of the intestine and rectum. The developmental cycle outside the human body consists of hatching of the ova in water and the liberation then of a free swimming miracidium resembling a paramecium. The miracidium is attracted to certain species of snails. In the incubation period a local cutaneous reaction consisting in petechial hemorrhages with an inflammatory reaction usually occurs at the point where the cercariae have penetrated. Several days later an urticarial rash may develop, with accompanying pronounced eosinophilia. After the ova have passed from the venules of the vesical plexus into the vesical wall, a pronounced degree of congestion of the mucous membrane occurs and is followed by necrosis and erosion. In the healing process the vesical wall becomes thickened due to the fibroblastic reaction, and crystalline deposits may form about the ova in the wall and mucous membrane.

Terminal hematuria is the outstanding sign of the disease. However, as this is common to many infections, great care in interrogation should bring out the fact that the patient has visited or resided in areas in which the infection is known to be present. Further inquiry may give a definite history of mild dermal involvement during or shortly following his sojourn, or the patient may even state that he has been in poor health, with recurrent attacks of mild fever and general malaise. Bleeding may be accompanied with irritation of the bladder or may be entirely

41. Peters, C. N.; Huntress, R. L., and Porter, J. E.: Urinary Schistosomiasis: Report of Two Cases in Maine, J. Urol. **54**:301-306 (Sept.) 1945.

painless, and in some periods the urine may be free from gross blood. Changes in the trigonal mucous membrane from the so-called velvety appearance to granulomatous involvement, even progressing to papillary growth and carcinomatous tumefaction, have been noted.

Antimony in the compound named fuadin has practically displaced all previous treatment. It is given intramuscularly or intravenously daily, and it is recommended that daily doses be increased. The dose starts at 1 cc. and is increased according to tolerance. The dose is leveled to 5 cc. every second day until 40 cc. has been given. Rarely a second course is necessary.

Two cases are reported in detail. In 1 case both Schistosoma haematobium and Schistosoma mansoni were found.

CHYLURIA

Yamauchi [42] reports the clinical, laboratory and statistical study of cases of chyluria. His report is based on the analysis of the records of 45 cases of chyluria which are carefully compared and correlated with those recorded in the literature.

Patients suffering from chyluria had all been exposed to Filaria in their lifetime, but filariae were never demonstrated in blood, urine or, in some cases, tissues. The long period elapsing from the last possible exposure to Filaria to the onset of chyluria in many of these cases, the absence of eosinophilia in the majority and several other factors indicate that filariasis probably predisposes to this condition but does not actually initiate it. This role, however, is real and definite, and any one who has been exposed to this nematode becomes a potential candidate for chyluria any time, even many years after the exposure.

Urinary stasis has been considered as the exciting cause of chyluria. Rupture of the fornix caused by urinary stasis results in a lymphaticourinary communication, and chyle appears in the voided urine if the ruptured lymphatic vessels already contain chyle. Except in a few instances minimal pathologic changes sufficient to form varices are probably present in the lymphatics without definite obstruction to the large retroperitoneal lymphatic vessels and thoracic duct. Pregnancy, endocervicitis and prostatic hypertrophy, so frequently found with this condition, become logical concomitant occurrences instead of bizarre associations when viewed in this light.

Chyluria is characterized by the appearance of chyle per se in the voided urine. The presence of fat granules in a colloidal state, the presence of albumin, erythrocytes and lymphocytes, the pyelographic injection of the renal and perirenal lymphatics frequently associated with

42. Yamauchi, S.: Chyluria: Clinical, Laboratory and Statistical Study of Forty-Five Personal Cases Observed in Hawaii, J. Urol. **54**:318-347 (Sept.) 1945.

rupture of the fornix and pyelovenous reflux and the control of the condition by repeated intrapelvic lavage with sclerosing solutions support the surmise that a lymphaticourinary fistula is present at the fornix of the calices.

The control of chyluria can be accomplished without much difficulty by repeated intrapelvic lavage with solutions of silver nitrate through inlaid catheters, but the cause of urinary stasis must be removed and fat in the diet must be limited after such lavages. The success of such management depends on the extent to which the predisposing and exciting causes can be eliminated.

DENGUE

Weyrauch and Glass,[43] in a study of 141 male patients recovering from dengue fever, found that in 8 cases (5.7 per cent) conclusive signs or history of involvement of the urogenital tract was present. Five patients suffered from dengue orchitis, and subsequent atrophy of the testis developed in 3 of these cases. Five patients experienced repeated bloody seminal emissions in the first few months of convalescence. In 2 cases, the latter finding was confirmed by laboratory examination of the spermatic fluid. It was noted that atrophy of the testis sometimes occurred following minimal swelling of the testis. This observation casts doubt on the common assumption that atrophy is caused by compression of the testis incident to tremendous engorgement within its inelastic capsule. Our studies indicate that an active pathologic process may persist in the urogenital tract for several months after the acute febrile phase of dengue fever, as evidenced by hemospermia and progressive atrophy of the testis.

REITER'S DISEASE

Colby [44] reviews 3 cases in which the essential features of the syndrome known as Reiter's disease were present. All 3 patients were young men. The typical triad of urethritis, conjunctivitis and arthritis was present. There is insufficient evidence that the disease is contracted by sexual exposure. Bacteriologic studies have failed to identify the causative agent. The course of the disease is unaffected by any known treatment, including penicillin. Instances of permanent articular disability are rare, although a few have been reported. Recurrent ocular, articular and urinary symptoms may occur. Renal complications may occur and be of considerable severity.

---

43. Weyrauch, H. M., and Glass, H.: Urogenital Complications of Dengue Fever, J. Urol. **55**:90-93 (Jan.) 1946.

44. Colby, F. H.: Renal Complications of Reiter's Disease, Tr. Am. A. Genito-Urin. Surgeons **37**:93-98, 1944.

HERMAPHRODITISM

McKenna and Kiefer [45] present 2 cases of true hermaphroditism. One child, 13 years old, had an ovotestis in the scrotum on the right side and an ovary in the inguinal canal on the left. A rudimentary vagina opened into the urethra and pronounced hypospadia was present. The second child, 3 years old, had a testis in the scrotum on the right side and an ovary on the left side of the abdomen, with a tube on the left side and a rudimentary vagina opening into the urethra. Hypospadia was also present. The second case is one of true lateral hermaphroditism, the first nearly so except for a small nodule of ovarian tissue attached to the testis. In each case the ovary was removed, and the testis was the only sex gland remaining.

OSTEITIS PUBIS

Cohen [46] presents 2 cases of osteitis pubis following suprapubic prostatectomy. Symptoms of osteitis pubis may develop as late as three months after operation, particularly when the condition is associated with delayed operative complications. Trêatment with penicillin and sulfonamide drugs did not appear to have any effect on the course of the disease. The clinical progress of osteitis pubis in the majority of instances would appear to indicate an aseptic process of the variety of Sudeck's atrophy, rather than osteomyelitis of the pubis. Roentgenologic findings and absence of response to treatment with the sulfonamide compounds and penicillin tend to confirm this. Orthopedic measures, such as traction or immobilization by a plaster of paris spica cast, usually will give gratifying relief of the pelvic pain.

Muschat [47] reports 2 cases of osteitis pubis following prostatectomy. He states that this condition occurs after operations on the urinary bladder and especially after prostatectomy. The disease begins about ten days after operation but may not begin until two months later. The pain usually starts over the symphysis, gradually shifting to the right or the left of the suprapubic area. Next the pain travels to the crotch, to the triangle of Scarpa and to the inner side of the thighs. Later in the disease there may be pain in the perineum and over the tuberosities of the ischii. The patient experiences excruciating pain in the inner side of the thighs in the form of spasmodic contractions of the adductor muscles. Recovery is slow and tedious, and improvement can be noted only after periods of weeks.

---

45. McKenna, C. M., and Kiefer, J. H.: Two Cases of True Hermaphroditism, Tr. Am. A. Genito-Urin. Surgeons **37**:21-26, 1944.

46. Cohen, H. H.: Osteitis Pubis, J. Urol. **55**:84-89 (Jan.) 1946.

47. Muschat, M.: Osteitis Pubis Following Prostatectomy, J. Urol. **54**:447-458 (Nov.) 1945.

The diagnosis is established by roentgenologic examination. Early in the disease no changes are seen. As the disease progresses (about the third week) the roentgenogram reveals some changes in the symphysis pubis; namely, fraying of the periosteum, with a moth-eaten appearance of the symphysis and the ramus pubis on either side. Later, more involvement of bone is seen. Decalcification involves the rami and the inner portions of the ischii until the tuberosities are reached. After eight to ten weeks, recalcification begins, with rapid reconstruction of the structure of the bone. The symphysis, however, remains separated and later becomes completely ankylosed by bone. The bacteria found varies in every case, but the predominant offenders appear to be Bacillus proteus, Esch. coli and hemolytic and nonhemolytic Staph. aureus. The clinical picture is clearcut and the roentgenologic evidence so definite that no difficulty should be encountered in making the correct diagnosis.

Muschat states that this disease is self limited and does not require surgical intervention. If an abscess does develop it should be drained properly. He used 4,000,000 units of penicillin in 1 case, without any subjective improvement. Sulfonamide drugs were administered and did not influence the condition. One thing must be borne in mind, that any manipulative procedure to hasten recovery is strongly contraindicated. It only aggravates the condition and stirs up local trauma, thus actually spreading the disease process and delaying recovery. The ultimate outcome in all these cases is good. The disease does not spread to other structures or organs. The only complication encountered is occasional formation of abscess with restitution after drainage. The only scar demonstrable is complete ossification and ankylosis of the symphysis. This fortunately remains symptomless.

ANURIA

Lattimer [48] discusses a plan for management of anuria. He analyzes the various methods of treatment which were used in his series of cases, and the most successful plan of action was selected from this experience. This regimen was followed in the management of his 7 most recent cases of anuria. All 7 patients have recovered. First and foremost, a warning sign was posted on the bed that the total intake of fluid was to be restricted to 1,000 to 1,300 cc. per twenty-four hours according to the patient's size and the temperature of the room. The degree of hydration, concentration of the serum proteins and the blood count were evaluated by determination of the hematocrit level, the specific gravity of the blood and the number of erythrocytes. Any abnormalities were corrected

48. Lattimer, J. K.: A Plan for the Management of Anuria, J. Urol. **54**: 312-317 (Sept.) 1945.

to normal levels by infusions of isotonic solution of sodium chloride or transfusions of blood or plasma as indicated by the studies of the blood.

Thorough alkalinization of the blood and urine was started at once, especially if there was reason to believe that anuria was due to sulfonamide drugs, transfusion reaction or toxins from traumatized tissues. An infusion of 1,000 cc. of 1.2 per cent solution of sodium bicarbonate in distilled water was started, and 4 Gm. of bicarbonate was given in water every three hours, by mouth and by rectum, until the carbon dioxide–combining power of the blood was elevated to levels of 70 to 90 volumes per hundred cubic centimeters. Whatever urine was then produced was usually alkaline. The p_H of every urine specimen was determined. A plain roentgenogram of the urinary tract was taken to exclude obstructing calculi from the diagnosis. Cystoscopy with the passage of small ureteral catheters and pyelography with one of the isotonic iodide solutions were advised for most anuric patients. In cases in which sulfonamide crystals were suspected, these examinations were made at once and the ureters and pelves lavaged for twenty minutes with warm 10 per cent solution of sodium bicarbonate. In other cases it was done at any time within the first two days in order to exclude the diagnosis of structural abnormality. In infants, cystoscopy was deferred as long as possible because of the usual need for general anesthesia. If mechanical obstruction was found, it was corrected at once by operation. Electrolyte levels were watched carefully. If the level of potassium in the serum rose to toxic levels, concentrated solution of sodium chloride or sodium bicarbonate was given. If the level of chlorides in the plasma dropped, sodium chloride was given in adequate doses, usually of 10 Gm. daily. If the sodium chloride was not tolerated by mouth or rectum, it was given intravenously. A high carbohydrate diet which contained a small proportion of protein was given. One or more doses of 50 per cent solution of dextrose were tried arbitrarily in the first two days of anuria. If renal function was not reestablished by these measures, a period of about fourteen days elapsed before further treatment was given if the patient's condition remained good. If anuria persisted after fourteen days of conservative treatment, bilateral renal decapsulation was considered. If cerebral or renal edema was already present, manifested by convulsions or decline in the patient's general condition, an earlier attempt at renal decapsulation might well be indicated. In the period of anuria, the greatest danger was from edema. Pulmonary edema and pleural effusions were complicated by bronchopneumonia, cerebral edema caused convulsions and renal edema led to further renal damage.

Hoffman and Colby [49] review the world literature on cases of incarceration of the penis and add a case, bringing the total number of reports to 114. The various motives involved and the types of constricting bands used are enumerated. An instrument for removing metal rings from the penis is described. The advisability of attempting repair by primary intention in the presence of adequate antisepsis is discussed and favored, and the role of lymphatic location in the satisfactory restoration of structure and function of the organ is suggested. The importance of psychologically intelligent handling of the patient for preservation of effective integrity is stressed.

ANTISEPTICS

Menville and Ross [50] stated that the response of gonorrhea to sulfonamide drugs is poor. Gonorrhea treated by the administration of urea in doses of 20, 40 and 60 Gm. daily in conjunction with the administration of sulfonamide drugs responds somewhat better than to sulfonamide drugs alone. The response to sulfonamide drugs with and without urea is greatest in cases in which no previous treatment has been given. The majority of the patients respond to the first course of treatment. The administration of urea in doses of 20, 40 and 60 Gm. daily apparently does not enhance treatment with sulfonamide drugs in cases of sulfonamide-resistant gonorrhea. Urea and sulfonamide compounds are in no way comparable to penicillin in the treatment of gonorrhea. The administration of urea in doses of 20, 40 and 60 Gm. daily does not appreciably elevate the concentration of urea in the urine. Doses of 20 Gm. of urea daily did not appreciably change the level of sulfonamide drugs in the blood in the small series of patients examined.

---

49. Hoffman, H. A., and Colby, F. H.: Incarceration of the Penis, J. Urol. **54**:391-399 (Oct.) 1945.

50. Menville, J. G., and Ross, C. W.: Urea and Sulfonamides in the Treatment of Gonorrhea, J. Urol. **54**:211-219 (Aug.) 1945.